

SEARCH REQUEST FORM

(for Mary Hale) Scientific and Technical Information Center

Requester's Full Name: BERCH Examiner #: 59193 Date: 8/7/02
Art Unit: 1624 Phone Number 30 84718 Serial Number: 091890741
Mail Box and Bldg/Room Location: 4D5 Results Format Preferred (circle): PAPER DISK E-MAIL
4E12

If more than one search is submitted, please prioritize searches in order of need.

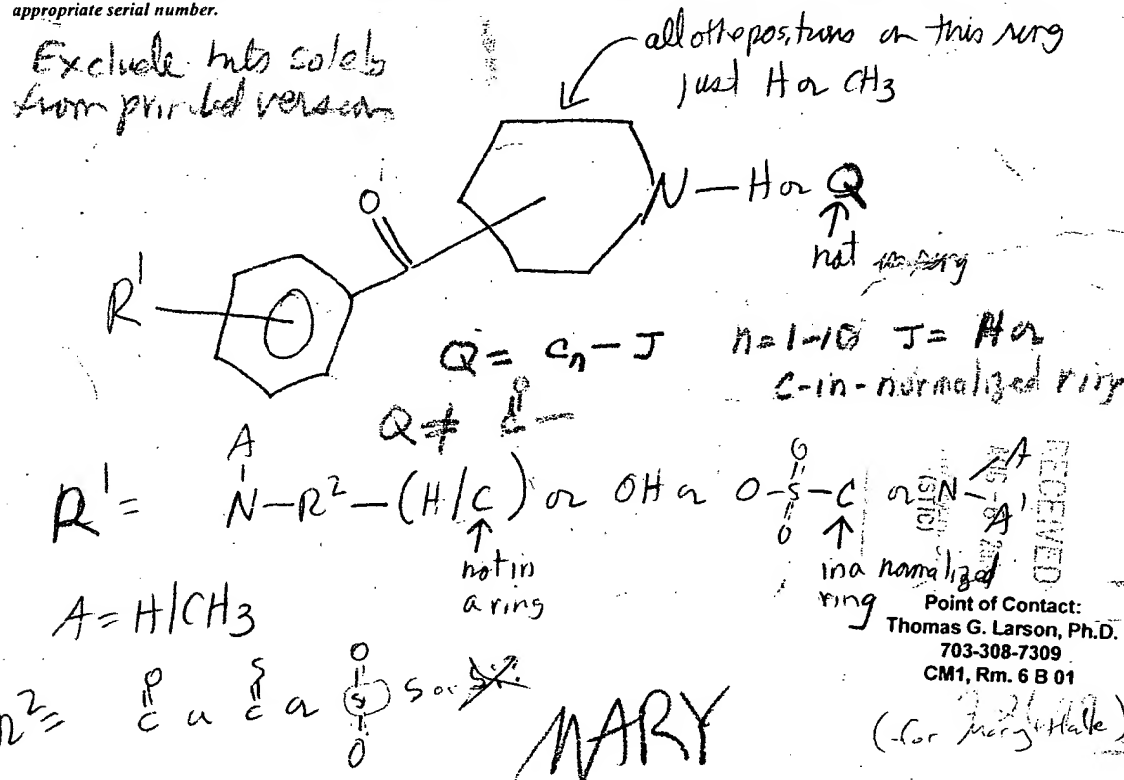
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.



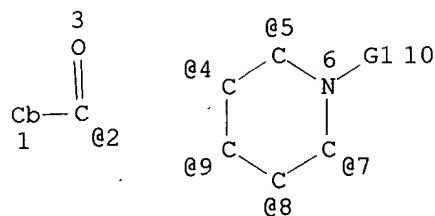
STAFF USE ONLY

| Staff Use Only | Type of Search | Vendors and cost where applicable |
|---|----------------------------|-----------------------------------|
| Searcher: <u>Thom Larson</u> | NA Sequence (#) <u>STN</u> | <u>\$1,809</u> |
| Searcher Phone #: <u>308-7309</u> | AA Sequence (#) | Dialog |
| Searcher Location: <u>6B01</u> | Structure (#) <u>1</u> | Questel/Orbit |
| Date Searcher Picked Up: <u>8/14/02</u> | Bibliographic | Dr. Link |
| Date Completed: <u>8/22/02</u> | Litigation | Lexis/Nexis |
| Searcher Prep & Review Time: <u>90</u> | Fulltext | Sequence Systems |
| Clerical Prep Time: | Patent Family | WWW/Internet |
| Online Time: <u>647</u> | Other | Other (specify) |

=> d que

L1

STR



VAR G1=H/C

VPA 2-4/5/7/8/9 SE

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

GGCAT IS MCY UNS AT 1

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS E6 C AT 1

GRAPH ATTRIBUTES:

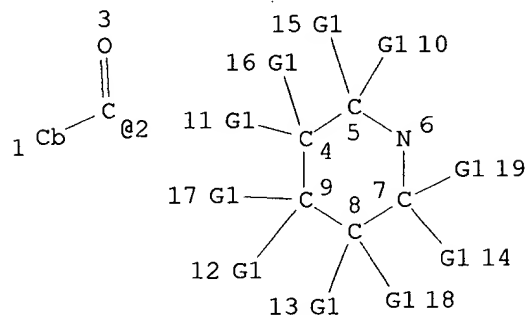
RSPEC I

NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE

L2

STR



VAR G1=2/H/ME

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

GGCAT IS MCY UNS AT 1

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS E6 C AT 1

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 19

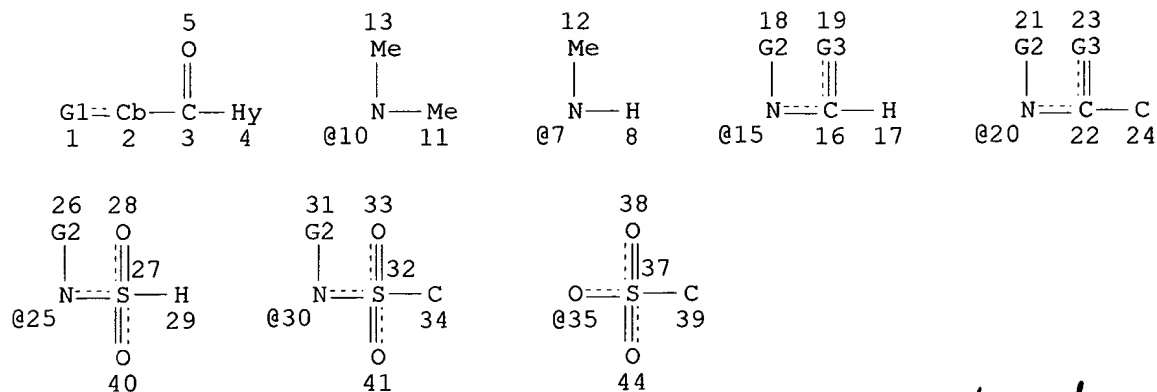
STEREO ATTRIBUTES: NONE

Substructure L1 - finds variable point of attachment of carboxyl group on piperidine ring where piperidine ring is substituted at nitrogen. Carbocyclic (cb) moiety on carboxyl group is limited to having 6 carbons and to being unsaturated

substructure L2 - allows carbons on piperidine ring to only be substituted by H/CH₃/Cb-C. Cb is limited as in sub-structure #1 above.

L3

STR



VAR G1=OH/NH2/7/10/15/20/25/30/35

VAR G2=H/ME

VAR G3=O/S

NODE ATTRIBUTES:

NSPEC IS C AT 24

NSPEC IS C AT 34

NSPEC IS R AT 39

DEFAULT MLEVEL IS ATOM

GGCAT IS MCY UNS AT 2

GGCAT IS MCY SAT AT 4

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS E6 C AT 2

ECOUNT IS E5 C E1 N AT 4

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

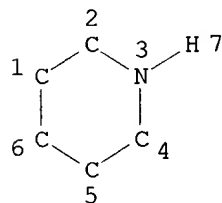
NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE

L4 (346008)SEA FILE=REGISTRY ABB=ON PLU=ON 46.150.18/RID AND 46.156.1/RI

L5 268 SEA FILE=REGISTRY SUB=L4 SSS FUL L1 AND L2 AND L3

L6 STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 7

STEREO ATTRIBUTES: NONE

sub structure L3

limits Cb to being
substituted at any position
by R'(G1)

Initial search (L4) create
a subset of all structures
in Registry having both a benzene
and piperidine ring using ring identifiers.

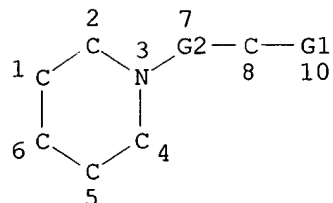
L5 - find all structures within
subset L4 meeting structural
requirements of substructures
1 & 2 & 3. This is the
answer set that I
showed to you.

(L6)
This substructure refines
the search by finding
structures where the
piperidine nitrogen has an
hydrogen substituent.

{ Sorry — This page turned out
blank due to a formatting
error }

L7

STR

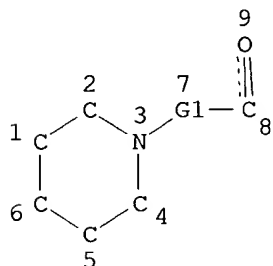


Cy @9

VAR G1=H/9
 REP G2=(0-9) C
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 GGCAT IS UNS AT 9
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
 L8 STR



REP G1=(0-9) C
 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 9

STEREO ATTRIBUTES: NONE

| | | | | | | | |
|-----|-----|-----|---------------|--------|--------|-----------------|----------|
| L9 | 252 | SEA | FILE=REGISTRY | SUB=L5 | SSS | FUL | L6 OR L7 |
| L10 | 61 | SEA | FILE=REGISTRY | SUB=L5 | SSS | FUL | L8 |
| L11 | 206 | SEA | FILE=REGISTRY | ABB=ON | PLU=ON | L9 NOT L10 | |
| L12 | 194 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L11 | |
| L13 | 1 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | WO2000047559/PN | |
| L14 | 193 | SEA | FILE=HCAPLUS | ABB=ON | PLU=ON | L12 NOT L13 | |

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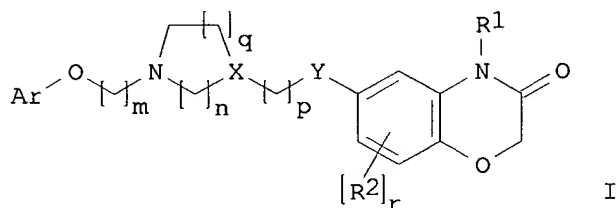
This substructure (L7) finds all piperidine rings substituted by $Q = C_n - J$ where $G_1 = J$ and $G_2 - C = C_n$.
 Cy @9 is limited to unsaturated to isolate normalized rings (cyclic moieties).

This sub-structure (L8) finds structures where the substituent on the piperidine moiety is substituted with a carbonyl group so that I can use the negation of the group to remove those structures from the answer set.

{ Search substruct in L5 for structures where piperidine N has substituents in L6/L7.
 { Remove structures with carbonyl.
 { Cross answers into HCAPLUS and remove inventors WO publication, thereby removing structures that only appear in it.

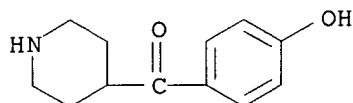
L14 ANSWER 1 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:332196 HCAPLUS
DOCUMENT NUMBER: 136:355241
TITLE: Preparation of benzoxazinones as antidepressants and
anxiolytics
INVENTOR(S): Johnson, Christopher Norbert; Rami, Harshad Kantilal;
Stemp, Geoffrey; Thewlis, Kevin; Thompson, Mervyn;
Vong, Antonio Kuok Keong
PATENT ASSIGNEE(S): Smithkline Beecham P.L.C., UK
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2002034754 | A2 | 20020502 | WO 2001-EP12344 | 20011022 |
| WO 2002034754 | A3 | 20020711 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| PRIORITY APPLN. INFO.: | | | GB 2000-26224 | A 20001026 |
| | | | GB 2001-11858 | A 20010515 |
| OTHER SOURCE(S): | MARPAT 136:355241 | | | |
| GI | | | | |



AB The title compds. [I; Ar = (un)substituted Ph, naphthyl, a monocyclic or a bicyclic heteroarom. group; when Ar = Ph or a monocyclic heteroarom. group, substituents positioned ortho to one another may be linked to form a 5-6 membered ring; R1 = H, alkyl, alkenyl, alkynyl, arylalkyl; R2 = halo, alkyl, CN, CF3, alkanoyl, alkoxy, OH; X = CH, N; Y = a single bond, O, CO; p = 0-2; r = 0-3; m = 2-4; n, q = 1-2], useful as medicaments for various CNS disorders, including depression and/or anxiety, were prepd. Thus, reacting 6-(4-piperidinyloxy)-4H-benzo[1,4]oxazin-3-one.HCl with 4-1H-indolyloxyacetaldehyde in the presence of NaBH(OAc)₃ in 1,2-dichloroethane afforded 63% I [Ar = 4-indolyl; R1 = H; X = CH; Y = O; p = 0; q = 1; n, m = 2; r = 0]. All compds. I tested according to the radioligand binding assay were found to have pK_i values > 6.0 at 5-HT1A receptors.

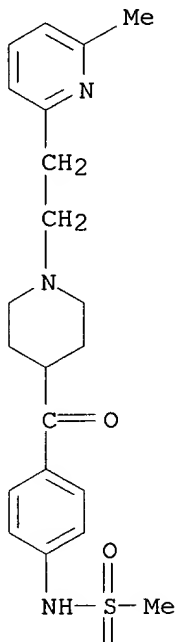
IT **420786-53-4P**, 4-(4-Hydroxybenzoyl)piperidine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(prepn. of benzoxazinones as antidepressants and anxiolytics)
RN 420786-53-4 HCAPLUS
CN Methanone, (4-hydroxyphenyl)-4-piperidiny- (9CI) (CA INDEX NAME)



L14 ANSWER 2 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:153988 HCAPLUS
DOCUMENT NUMBER: 137:15531
TITLE: The binding site for channel blockers that rescue
misprocessed human long QT syndrome type 2
ether-a-gogo-related gene (HERG) mutations
AUTHOR(S): Ficker, Eckhard; Obejero-Paz, Carlos A.; Zhao, Shuxia;
Brown, Arthur M.
CORPORATE SOURCE: Rammelkamp Center for Education and Research, Case
Western Reserve University, Cleveland, OH, 44109, USA
SOURCE: Journal of Biological Chemistry (2002), 277(7),
4989-4998
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular
Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in the human ether-a-gogo-related gene (HERG) K⁺ channel gene
cause chromosome 7-linked long QT syndrome type 2 (LQT2), which is
characterized by a prolonged QT interval in the ECG and an increased
susceptibility to life-threatening cardiac arrhythmias. LQT2 mutations
produce loss-of-function phenotypes and reduce I_{Kr} currents either by the
heteromeric assembly of non- or malfunctioning channel subunits with wild
type subunits at the cell surface or by retention of misprocessed mutant
HERG channels in the endoplasmic reticulum. Misprocessed mutations often
encode for channel proteins that are functional upon incorporation into
the plasma membrane. As a result the pharmacol. correction of folding
defects and restoration of protein function are of considerable interest.
Here we report that the trafficking-deficient pore mutation HERG G601S was
rescued by a series of HERG channel blockers that increased cell surface
expression. Rescue by these pharmacol. chaperones varied directly with
their blocking potency. We used structure-activity relationships and
site-directed mutagenesis to define the binding site of the pharmacol.
chaperones. We found that binding occurred in the inner cavity and
correlated with hydrophobicity and cationic charge. Rescue was
domain-restricted because the trafficking of two misprocessed mutations in
the C terminus, HERG F805C and HERG R823W, was not restored by channel
blockers. Our findings represent a first step toward the design of
pharmacol. chaperones that will rescue HERG K⁺ channels without block.
IT **113559-13-0**, E 4031
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(binding site for channel blockers that rescue misprocessed human long

QT syndrome type 2 ether-a-gogo-related gene (HERG) mutations)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:896641 HCAPLUS

DOCUMENT NUMBER: 137:72899

TITLE: Potassium channel blocker activates extracellular signal-regulated kinases through Pyk2 and epidermal growth factor receptor in rat cardiomyocytes

AUTHOR(S): Tahara, Satoko; Fukuda, Keiichi; Kodama, Hiroaki; Kato, Takahiro; Miyoshi, Shunichiro; Ogawa, Satoshi
CORPORATE SOURCE: Cardiopulmonary Division, Keio University School of Medicine, Tokyo, Japan

SOURCE: Journal of the American College of Cardiology (2001),

Searched by Thom Larson, STIC, 308-7309

38(5), 1554-1563
CODEN: JACCDI; ISSN: 0735-1097
Elsevier Science Inc.

PUBLISHER:
DOCUMENT TYPE:
LANGUAGE:

Journal
English

AB OBJECTIVES We sought to det. whether potassium (K+) channel blockers (KBs) can activate extracellular signal-regulated kinase (ERK) and to characterize the upstream signals leading to ERK activation in cardiomyocytes. BACKGROUND Because KBs attenuate K+ outward current, they may possibly prolong the duration of action potentials, leading to an increase in calcium (Ca2+) transient ([Ca2+]i) in cardiomyocytes. Elevation of intracellular Ca2+ levels can trigger various signaling events. Influx of Ca2+ through L-type Ca2+ channels after membrane depolarization induced activation of MEK and ERK through activation of Ras in neurons. Although KBs are frequently used to treat cardiac arrhythmias, their effect on signaling pathways remains unknown. METHODS Primary cultured rat cardiomyocytes were stimulated with four different KBs, 4-aminopyridine (4-AP), E-4031, tetra-ethylammonium and quinidine, and phosphorylation of ERK, proline-rich tyrosine kinase 2 (Pyk2) and epidermal growth factor receptor (EGFR) was detected. Action potentials were recorded by use of a conventional microelectrode. (Ca2+)i was monitored by the fluorescent calcium indicator Fluo-4. RESULTS E-4031, 4-AP, tetra-ethylammonium and quinidine induced phosphorylation of ERK. 4-Aminopyridine prolonged the duration of action potentials by 37% and increased (Ca2+)i by 52% at 1 mmol/l. Pre-incubation of ethyleneglycoltetraacetic acid, 1,2-bis(2-aminophenoxy)-ethane-N,N,N',N'-tetraacetic acid tetrakis and diltiazem completely blocked this phosphorylation, whereas flufenamic acid and benzamil did not. 4-Aminopyridine induced tyrosine phosphorylation of Pyk2 and EGFR, which peaked at 5 and 10 min, resp. Cytochalasin D, AG1478 and dominant-neg. EGFR strongly inhibited the phosphorylation of ERK, whereas calphostin C, calmidazolium and KN62 did not. CONCLUSIONS These findings indicate that KBs induce ERK activation, which starts with Ca2+ entry through the L-type Ca2+ channel in cardiomyocytes, and that EGFR and Pyk2 are involved in this activation.

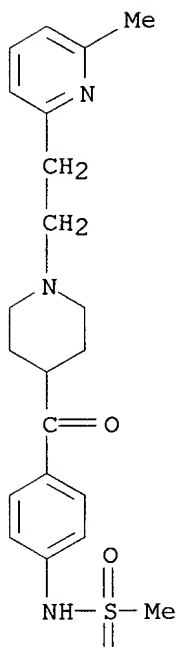
IT 113559-13-0, E-4031

RL: PAC (Pharmacological activity); BIOL (Biological study)
(potassium channel blocker activates extracellular signal-regulated kinases through Pyk2 and epidermal growth factor receptor in rat cardiomyocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:888622 HCAPLUS

DOCUMENT NUMBER: 136:177857

TITLE: Effects of different types of K⁺ channel modulators on the spontaneous myogenic contraction of guinea-pig urinary bladder smooth muscle

AUTHOR(S): Imai, T.; Okamoto, T.; Yamamoto, Y.; Tanaka, H.; Koike, K.; Shigenobu, K.; Tanaka, Y.

CORPORATE SOURCE: Department of Pharmacology, Toho University School of Pharmaceutical Sciences, Funabashi-City, 274-8510, Japan

SOURCE: Acta Physiologica Scandinavica (2001), 173(3), 323-333
CODEN: APSCAX; ISSN: 0001-6772

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

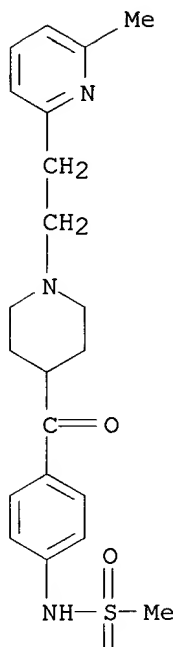
AB In the present study, the effects of different types of K⁺ channel modulators on the spontaneous rhythmic contractile activity were examd. in guinea-pig urinary smooth muscle (UBSM). Guinea-pig UBSM exhibited myogenic rhythmic contraction in the presence of atropine (1 .mu.M), phentolamine (1 .mu.M), propranolol (1 .mu.M), suramin (10 .mu.M), and tetrodotoxin (1 .mu.M). Nisoldipine (100 nM) or diltiazem (10 .mu.M) substantially diminished UBSM contractile activity. Nisoldipine-resistant component of UBSM rhythmic contraction was further inhibited by gadolinium (200 .mu.M). Iberiotoxin (50 nM), a selective blocker of large-conductance, voltage-gated Ca²⁺-activated K⁺ (KCa) (BK) channel, dramatically increased both contraction amplitude and frequency whereas NS-1619 (30 .mu.M), which increases BK channel activity, decreased them. Apamin (100 nM), a selective blocker of small-conductance, KCa (SK) channel, increased contraction amplitude but decreased frequency. A blocker of voltage-gated K⁺ (Kv) channel, 4-aminopyridine (100 .mu.M), significantly increased contraction frequency. E-4031, a blocker of a novel inwardly rectifying K⁺ channel, i.e. the human ether-a-go-go-related gene (HERG) K⁺ channel, significantly increased contraction amplitude. Glibenclamide (1-10 .mu.M) (KATP channel blocker) and Ba²⁺ (10 .mu.M) (conventional Kir channel blocker) did not exhibit conspicuous effects on spontaneous contractile activity of UBSM. These findings imply that 2 types of KCa (BK and SK) channels have prominent roles as neg. feedback elements to limit extracellular Ca²⁺ influx-mediated guinea-pig UBSM contraction by regulating both amplitude and frequency. It was also suggested that both non-KCa type of K⁺ (Kv and HERG-like K⁺) channels may contribute to the regulation of UBSM myogenic rhythmic contraction.

IT 113559-13-0, E-4031
RL: PAC (Pharmacological activity); BIOL (Biological study)
(effects of different types of potassium channel modulators on spontaneous myogenic contraction of guinea-pig urinary bladder smooth muscle)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:858033 HCAPLUS

DOCUMENT NUMBER: 136:353498

TITLE: Ionic remodeling of cardiac Purkinje cells by congestive heart failure

AUTHOR(S): Han, Wei; Chartier, Denis; Li, Danshi; Nattel, Stanley
CORPORATE SOURCE: Department of Medicine, Montreal Heart Institute, University of Montreal, Montreal, QC, Can.

SOURCE: Circulation (2001), 104(17), 2095-2100

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cardiac Purkinje cells (PCs) are important for the generation of triggered arrhythmias, particularly in assocn. with abnormal repolarization. The effects of congestive heart failure (CHF) on the ionic properties of PCs

are unknown. PCs were isolated from false tendons of control dogs and dogs with ventricular tachypacing-induced CHF. CHF PCs were hypertrophied (capacitance, mean \pm SEM, 149 \pm 4 pF, n = 130; vs. 128 \pm 3 pF, n = 150, control; $P < 0.001$). Transient outward c.d. was reduced in CHF PCs without change in voltage dependence or kinetics. CHF also reduced inward-rectifier c.d., with no change in form of the current-voltage relationship. Densities of L- and T-type calcium, rapid and slow delayed rectifier, and Na⁺-Ca²⁺ exchange currents were unaltered by CHF, but L-type calcium current inactivation was slowed at pos. potentials. Purkinje fiber action potentials from CHF dogs showed decreased phase 1 amplitudes and elevated plateau voltages and demonstrated twice as much prolongation on exposure to the rapid delayed rectifier blocker E-4031 as control Purkinje fibers. -CHF causes remodeling of important K⁺ and Ca²⁺ currents in cardiac PCs, decreasing repolarization reserve and causing an exaggerated repolarization delay in response to a class III drug. These results have important potential implications regarding ventricular arrhythmogenesis, particularly related to triggered activity in PCs, in patients with CHF.

IT **113559-13-0**, E-4031

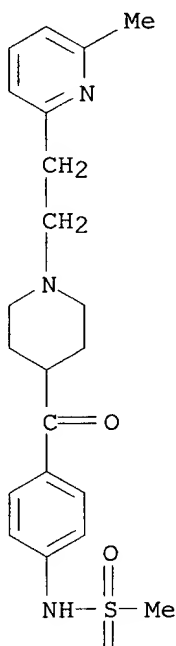
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cardiac Purkinje cells ionic remodeling in congestive heart failure in response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:827690 HCAPLUS

DOCUMENT NUMBER: 136:161081

TITLE: Inhibitory effect of bepridil on hKv1.5 channel current: comparison with amiodarone and E-4031

AUTHOR(S): Kobayashi, Satoru; Reien, Yoshie; Ogura, Takehiko; Saito, Toshihiro; Masuda, Yoshiaki; Nakaya, Haruaki

CORPORATE SOURCE: Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, Chuo-ku, Chiba, 260-8670, Japan

SOURCE: European Journal of Pharmacology (2001), 430(2-3), 149-157

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effects of bepridil on the depolarization-activated outward K⁺ currents (I_{out}) in rat atrial myocytes and the human cardiac K⁺ (hKv1.5) channel current stably expressed in human embryonic kidney (HEK) 293 cells were examd., and compared with those of amiodarone and N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl] methanesulfonamide dihydrochloride dihydrate (E-4031). Membrane currents were recorded using patch-clamp techniques in enzymically isolated rat atrial myocytes and HEK 293 cells expressing hKv1.5 channels. Bepridil potently inhibited I_{out} elicited by depolarization pulses and prolonged the action potential in rat atrial cells. Bepridil also inhibited the hKv1.5 channel current with the IC₅₀ value of 6.6 .mu.M. The inhibitory effects of bepridil on the currents in HEK 293 cells were voltage-dependent. Amiodarone weakly inhibited rat atrial I_{out} and hKv1.5 channel current. In contrast, E-4031 at a concn. of 10 .mu.M had little influence on these currents. Thus, bepridil inhibits hKv1.5 channel current and the inhibitory effect may be useful for the treatment of atrial fibrillation.

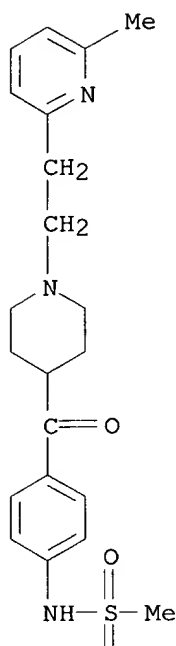
IT 113559-13-0, E-4031

RL: PAC (Pharmacological activity); BIOL (Biological study)
(inhibitory effect of bepridil on hKv1.5 channel current and comparison with amiodarone and E-4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:811210 HCAPLUS

DOCUMENT NUMBER: 136:144934

TITLE: [3H]Dofetilide binding to HERG transfected membranes: a potential high throughput preclinical screen

AUTHOR(S): Finlayson, Keith; Turnbull, Lorna; January, Craig T.; Sharkey, John; Kelly, John S.

CORPORATE SOURCE: Fujisawa Institute of Neuroscience, University of Edinburgh, Edinburgh, EH8 9JZ, UK

SOURCE: European Journal of Pharmacology (2001), 430(1), 147-148

CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacol. characteristics of [3H]dofetilide binding were examd. in

Searched by Thom Larson, STIC, 308-7309

membranes prepd. from human embryonic kidney (HEK293) cells stably expressing human ether-a-go-go related gene (HERG) K⁺ channels. The class III antiarrhythmic compds. dofetilide, clofilium, 4'-[[1-[2-(6-methyl-2-pyridyl)ethyl]-4-piperidyl]carbonyl]methanesulfonanilide (E-4031), N-methyl-N-[2-[methyl-(1-methyl-1H-benzimidazol-2-yl)amino]ethyl]-4-[(methylsulfonyl)amino]benzene-sulfonamide (WAY-123,398) and d-sotalol all inhibited [3H]dofetilide binding. In addn., the structurally unrelated compds. pimozide, terfenadine and haloperidol, all of which prolong the QT interval in man, also inhibited binding. These data indicate that a [3H]dofetilide binding assay using HERG membranes may help identify compds. that prolong the QT interval.

IT **113559-13-0**, E-4031

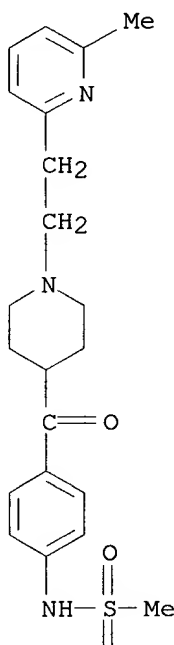
RL: PAC (Pharmacological activity); BIOL (Biological study)

([3H]dofetilide binding to HERG transfected membranes as potential high throughput preclin. screen)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2001:781179 HCAPLUS
 DOCUMENT NUMBER: 135:327349
 TITLE: Genetic diagnosis for QT interval prolongation related to adverse drug reactions
 INVENTOR(S): Woosley, Raymond L.
 PATENT ASSIGNEE(S): Georgetown University, USA
 SOURCE: PCT Int. Appl., 77 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2001079554 | A1 | 20011025 | WO 2001-US12087 | 20010413 |
| W: CA, JP, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |

PRIORITY APPLN. INFO.: US 2000-196916P P 20000413

AB The invention discloses methods of diagnosing whether an individual is predisposed to a prolonged QT interval or acquired long QT syndrome (LQTS) due to drug adverse reactions. In particular, the invention discloses that the diagnosis is genetic anal. of at least two polymorphisms or mutations of an individual, which are assocd. with an increased risk for prolonged QT intervals or Torsades de Pointes (TdP). Genetic screening for detg. the predisposition of prolonged QT intervals induced by a pharmaceutical agent is performed by identifying genetic polymorphisms or mutations located in at least two classes of genes, wherein the genes are (1) LQT genes, (2) altered sensitivity genes (e.g., MiRP1) or (3) increased exposure genes (e.g., MDR genes or P 450 cytochrome genes). The invention provides methods of screening pharmaceutical agents for their ability to induce prolonged QT interval or LQTS. The invention also provides compns. and kits for detg. such predispositions to adverse drug reactions.

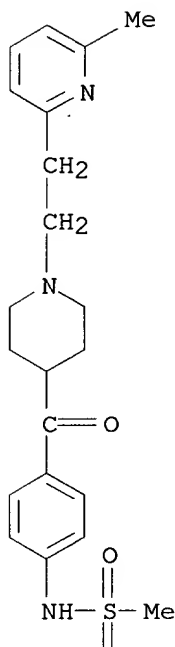
IT 113559-13-0, E-4031

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
 (genetic diagnosis for QT interval prolongation related to adverse drug reactions)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:775979 HCAPLUS

DOCUMENT NUMBER: 136:48654

TITLE: Ceramide inhibits the inwardly rectifying potassium current in GH3 lactotrophs

AUTHOR(S): Wu, Sheng-Nan; Lo, Yuk-Keung; Kuo, Benjamin Ing-Tiau; Chiang, Hung-Ting

CORPORATE SOURCE: Departments of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan

SOURCE: Endocrinology (2001), 142(11), 4785-4794
CODEN: ENDOAO; ISSN: 0013-7227

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of ceramide on ion currents in rat pituitary GH3 cells were

Searched by Thom Larson, STIC, 308-7309

investigated. Hyperpolarization-elicited K⁺ currents present in GH3 cells were studied to det. the effect of ceramide and other related compds. on the inwardly rectifying K⁺ current (IK(IR)). Ceramide (C2-ceramide) suppressed the amplitude of IK(IR) in a concn.-dependent manner, with an IC50 value of 5 .mu.M. Ceramide caused a right-ward shift in the midpoint for the activation curve of IK(IR). Pretreatment with PD-98059 (30 .mu.M) or U-0126 (30 .mu.M) did not prevent ceramide-mediated inhibition of IK(IR). However, the magnitude of ceramide-induced inhibition of IK(IR) was attenuated in GH3 cells preincubated with dithiothreitol (10 .mu.M). TNF.alpha. (100 ng/g) also suppressed IK(IR). In the inside-out configuration, application of ceramide (30 .mu.M) to the bath slightly suppressed the activity of large conductance Ca²⁺-activated K⁺ channels. Under the current clamp mode, ceramide (10 .mu.M) increased the firing of action potentials. Cells that exhibited an irregular firing pattern were converted to those displaying a regular firing pattern after application of ceramide (10 .mu.M). Ceramide also suppressed IK(IR) in neuroblastoma IMR-32 cells. Therefore, ceramide can produce a depressant effect on IK(IR). The blockade of this current by ceramide may affect cell function.

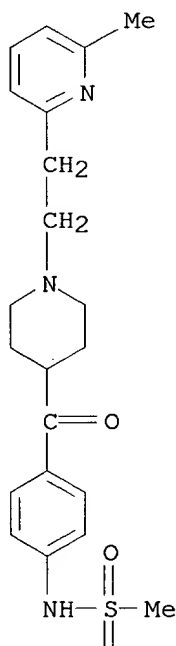
IT 113559-13-0, E-4031

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ceramide and related compds effects on inwardly rectifying potassium current in GH3 lactotrophs in relation to prolactin secretion)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:759383 HCAPLUS

DOCUMENT NUMBER: 136:112210

TITLE: An amino acid residue whose change by mutation affects drug binding to the HERG channel

AUTHOR(S): Ishii, K.; Kondo, K.; Takahashi, M.; Kimura, M.; Endoh, M.

CORPORATE SOURCE: Department of Pharmacology, Yamagata University School of Medicine, Yamagata, 990-9585, Japan

SOURCE: FEBS Letters (2001), 506(3), 191-195

CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We did the expts. to search for amino acids that affect quinidine binding to the HERG channel, and have identified an amino acid whose change by mutation affects the binding of various drugs. The residue is located at position 647 in the S6 and is not involved in the recently identified methanesulfonanilide binding pocket. The homol. model of the HERG channel indicated that the residue faces toward the outside of the channel pore. We conclude that the residue at position 647 does not interact directly with drug mols. but plays an important role in keeping the binding site's high affinity for drugs.

IT 113559-13-0, E-4031

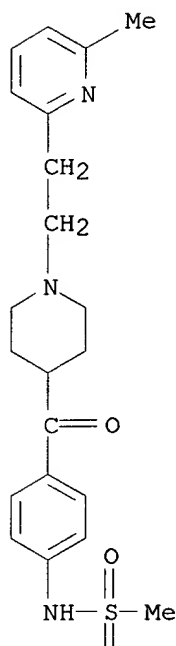
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(change of isoleucine-647 by mutation affects drug binding to the HERG channel)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:699657 HCAPLUS
DOCUMENT NUMBER: 136:31272
TITLE: Pharmacokinetic/pharmacodynamic assessment of the effects of E4031, cisapride, terfenadine, and terodiline on monophasic action potential duration in dog
AUTHOR(S): Webster, R.; Allan, G.; Anto-Awuakye, K.; Harrison, A.; Kidd, T.; Leishman, D.; Phipps, J.; Walker, D.
CORPORATE SOURCE: Department of Drug Metabolism, Pfizer Global Research and Development, Sandwich, CT13 9NJ, UK
SOURCE: Xenobiotica (2001), 31(8/9), 633-650
CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

AB 1. Torsades de pointes (TDP) is a potentially fatal ventricular tachycardia assocd. with increases in QT interval and monophasic action potential duration (MAPD). TDP is a side-effect that has led to withdrawal of several drugs from the market (e.g. terfenadine and terodiline). 2. The potential of compds. to cause TDP was evaluated by monitoring their effects on MAPD in dog. Four compds. known to increase QT interval and cause TDP were investigated: terfenadine, terodiline, cisapride, and E4031. On the basis that only free drug in the systemic circulation will elicit a pharmacol. response target, free concns. in blood plasma were selected to mimic the free drug exposures in man. Infusion regimens were designed that rapidly achieved and maintained target-free concns. of these drugs in plasma and data on the relationship between free concn. and changes in MAPD were obtained for these compds. 3. These data indicate that the free ED50 in plasma for terfenadine (1.9 nM), terodiline (76 nM), cisapride (11 nM), and E4031 (1.9 nM) closely correlate with the free concn. in man causing QT effects. For compds. that have shown TDP in the clinic (terfenadine, terodiline, cisapride) there is little differentiation between the dog ED50 and the efficacious free plasma concns. in man (<10-fold) reflecting their limited safety margins. These data underline the need to maximize the therapeutic ratio with respect to TDP in potential development candidates and the importance of using free drug concns. in pharmacokinetic/pharmacodynamic studies.

IT 113559-13-0, E4031

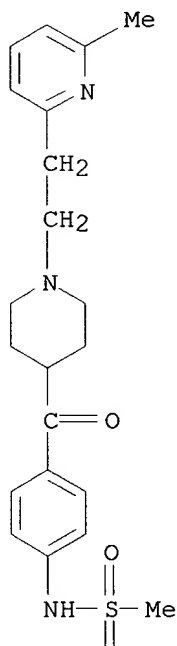
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacokinetic/pharmacodynamic assessment of effects of various drugs on monophasic action potential duration in dog)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:696519 HCAPLUS

DOCUMENT NUMBER: 136:241370

TITLE: Density and kinetics of IKr and IKs in guinea pig and
rabbit ventricular myocytes explain different efficacy
of IKs blockade at high heart rate in guinea pig and
rabbit. Implications for arrhythmogenesis in humans

AUTHOR(S): Lu, Zhibo; Kamiya, Kaichiro; Opthof, Tobias; Yasui,
Kenji; Kodama, Itsuo

CORPORATE SOURCE: Department of Circulation, Division of Regulation of
Organ Function, Research Institute of Environmental
Medicine, Nagoya University, Nagoya, 464-8601, Japan

SOURCE: Circulation (2001), 104(8), 951-956

CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background - Class III antiarrhythmic agents commonly exhibit reverse
frequency-dependent prolongation of the action potential duration (APD).
This is undesirable because of the danger of bradycardia-related
arrhythmias and the limited protection against ventricular
tachyarrhythmias. The effects of blockade of sep. components of delayed
rectifier K⁺ current (IK) may help to develop agents effective at high
heart rate. Methods and Results - We assessed the d. and kinetics of the
2 components of the delayed rectifier K⁺ current, IKr and IKs, in rabbit
and guinea pig ventricular myocytes. The effects of their specific
blockers (chromanol 293B for IKs and E-4031 for IKr) on the action
potential was studied at different heart rates by use of whole-cell
patch-clamp techniques. In guinea pig ventricular myocytes only, blockade
of IKs causes APD prolongation in a frequency-independent manner, whereas
blockade of IKs in rabbit ventricular myocytes shows reverse frequency
dependence, as does blockade of IKr in both species. This result can be
explained primarily by the higher d. of IKs in guinea pig ventricle and by
its slow deactivation kinetics, which allows IKs to accumulate at high
heart rate because little time is available for complete deactivation of
it during diastole. Conclusions - D. and kinetics of components of IK
explain why blockade of IKs is more effective at high heart rate in the
guinea pig ventricle than in the rabbit ventricle, without adverse effects
at low heart rate.

IT 113559-13-0, E-4031

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

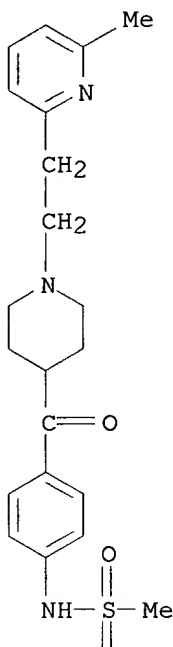
Searched by Thom Larson, STIC, 308-7309

(d. and kinetics of IKr and IKs in guinea pig and rabbit ventricular myocytes explain different efficacy of IKs blockade at high heart rate)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:653711 HCAPLUS

DOCUMENT NUMBER: 136:48203

TITLE: Interaction of azimilide with neurohumoral and channel receptors

AUTHOR(S): Brooks, R. R.; Pong, S. F.; Izzo, N. J.; Moorehead, T. J.; Gopalakrishnan, M.; Triggle, D. J.

CORPORATE SOURCE: Procter & Gamble Pharmaceuticals, Cincinnati, OH, 45252, USA

SOURCE: Biochemical Pharmacology (2001), 62(7), 883-892

Searched by Thom Larson, STIC, 308-7309

CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Binding of the class III antiarrhythmic agent azimilide to brain, heart, and other organ receptors was assessed by std. radioligand binding techniques. In a survey of 60 receptors, azimilide at 10 μ M inhibited binding by more than 50% at serotonin uptake (K_i : 0.6 μ M), muscarinic (K_i : 0.9 to -3.0 μ M), Na^+ channel site 2 (K_i : 4.3 μ M), and central sigma (K_i : 6.2 μ M) sites. Lesser (20-40%) inhibition was seen at adrenergic, histamine, serotonin, purinergic, angiotensin II, dopamine uptake, and norepinephrine sites and at a voltage-sensitive K^+ channel. In rat ventricle, azimilide inhibited binding to α_1 - and β -adrenergic and muscarinic receptors (K_i : <5 μ M) and to the L-type Ca^{2+} channel (K_i : 37.3 μ M). In rat brain, azimilide blocked ligand binding to these same receptors and to a serotonin receptor, and the breadth and potency of its interaction pattern differentiated it from ten other class III antiarrhythmics. Azimilide displayed agonist and antagonist action at five muscarinic receptor subtypes in transfected NIH 3T3 cells producing receptor-sensitive mitogenesis and β -galactosidase activity. Agonist action predominated at M2 and M4 subtypes, and antagonist action predominated at M1, M3, and M5 subtypes. The azimilide concn. for 50% max. stimulation (EC_{50}) in M2-expressing cells was 1.97 μ M (vs 0.14 μ M for carbachol). Azimilide's receptor interactions occur at concns. from one to forty times those required to block cardiac delayed-rectifier channels but could contribute to the efficacy and safety of the drug.

IT 113559-13-0, E 4031

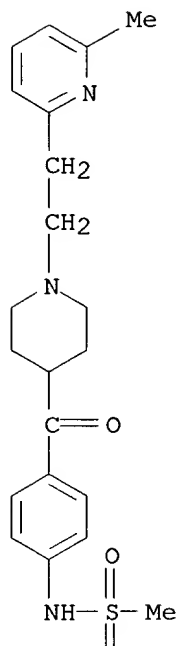
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(interaction of class III antiarrhythmics with brain membrane receptors)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2001:616775 HCAPLUS
 DOCUMENT NUMBER: 136:95797
 TITLE: Three thiadiazinone derivatives, EMD 60417, EMD 66430, and EMD 66398, with class III antiarrhythmic activity but different electrophysiologic profiles
 AUTHOR(S): Himmel, Herbert M.; Wettwer, Erich; Lues, Inge; Beier, Norbert; Jonas, Rochus; Ravens, Ursula
 CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dresden University of Technology, Dresden, D-01307, Germany
 SOURCE: Journal of Cardiovascular Pharmacology (2001), 38(3), 438-449
 CODEN: JCPCDT; ISSN: 0160-2446
 PUBLISHER: Lippincott Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

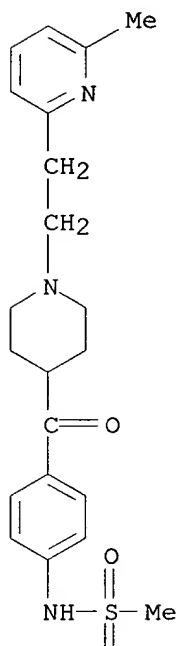
AB The thiadiazinone derivs. EMD 60417, EMD 66430, and EMD 66398 were developed as class III antiarrhythmic agents. Their chem. structure is closely related to that of their calcium-sensitizing congener [+] -EMD 60263, and EMD 66398 possesses the methylsulfonylaminobenzoyl moiety present in the prototypical IKr blocker E-4031. We compared the electrophysiol. effects of these compds. with std. drugs (almokalant, E-4031, quinidine) in cardiac myocytes from guinea-pig ventricle and human atrium by whole-cell patch-clamp technique. The test compds.' class III action, which is related to impairment of K⁺ channel function, was confirmed by action potential measurements. EMD 60417, EMD 66430, EMD 66398, and almokalant (1 .mu.M each) reversibly prolonged the action potential duration in guinea-pig myocytes. In the same cells, the rapidly activating component IKr of the delayed rectifier K⁺ current, which has been defined by its sensitivity to E-4031, was reduced by EMD 60417, EMD 66430, EMD 66398, and almokalant. Inhibition of IKr was concn.-dependent as detd. by attenuation of tail currents. The slowly activating component IKs of the delayed rectifier K⁺ current was not affected. The inward rectifier K⁺ current IK1 was not influenced at potentials close to the reversal potential. Transient and sustained outward K⁺ currents (Ito, Iso) measured in human atrial myocytes were not altered by any EMD compd. L-type Ca²⁺ current was hardly affected at concns. of 1-10 .mu.M, but sodium current was decreased. Action potential prolongation by EMD 60417, EMD 66430, and EMD 66398 is due to block of IKr. INa is inhibited at higher concns. by EMD 66430 and EMD 60417. EMD 66398 is more potent and selective for IKr than EMD 60417 and EMD 66430, and thus resembles E-4031 in structure and function.

IT **113559-13-0**, E-4031
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison std.; three thiadiazinone derivs., EMD 60417, EMD 66430, and EMD 66398, with class III antiarrhythmic activity but different electrophysiol. profiles)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2001:493776 HCAPLUS
 DOCUMENT NUMBER: 135:164876
 TITLE: Molecular cloning and expression of cERG, the ether a go-go-related gene from canine myocardium
 AUTHOR(S): Zehelein, Jorg; Zhang, Wei; Koenen, Michael; Graf, Michael; Heinemann, Stefan H.; Katus, Hugo A.
 CORPORATE SOURCE: Innere Medizin III, Universitätsklinik Heidelberg, Heidelberg, 69115, Germany
 SOURCE: Pfluegers Archiv (2001), 442(2), 188-191
 CODEN: PFLABK; ISSN: 0031-6768
 PUBLISHER: Springer-Verlag
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Given the anatomical and physiol. similarities to the human heart, canine in vivo heart models may facilitate the anal. of mol. mechanisms

Searched by Thom Larson, STIC, 308-7309

underlying cardiac repolarization abnormalities. The development of such models depends, however, on information about canine K⁺ channels responsible for the establishment of IK currents. In this context, the authors isolated and sequenced the reverse transcript of the canine ether a go-go-related gene (cERG). The complementary DNA (cDNA)-derived cERG polypeptide consists of 1,158 amino acids, the sequence of which shows striking homol. to human, rat and mouse ERG subunits (97%, 94% and 95% identity resp.). In highly conserved peptide domains like the PAS domain, the membrane-spanning segments S1, S3-S6 and the pore-forming region, there was 100% identity. Anal. of cERG transcription revealed abundant expression of cERG mRNA in heart and brain and low expression in liver, spleen and kidney. Membrane currents recorded in *Xenopus* oocytes expressing cERG channels showed functional properties very similar to the human K⁺ channel hERG, which encodes the .alpha.-subunit of the cardiac rapidly activating, delayed rectifier (IKr) channel.

IT 113559-13-0, E-4031

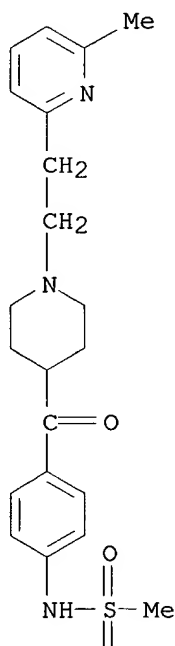
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mol. cloning, tissue expression, and functional properties of cERG, ether a go-go-related gene from canine myocardium in relation to antiarrhythmic effect)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:315374 HCAPLUS

DOCUMENT NUMBER: 135:162311

TITLE: Interactions between antiarrhythmic drugs and cardiac memory

AUTHOR(S): Plotnikov, A. N.; Shvilkin, A.; Xiong, W.; de Groot, J. R.; Rosenshtraukh, L.; Feinmark, S.; Gainullin, R.; Danilo, P.; Rosen, M. R.

CORPORATE SOURCE: Departments of Pharmacology and Pediatrics, Center for Molecular Therapeutics, College of Physicians and Surgeons of Columbia University, New York, NY, USA

SOURCE: Cardiovascular Research (2001), 50(2), 335-344

CODEN: CVREAU; ISSN: 0008-6363

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ventricular pacing or arrhythmias can induce cardiac memory (CM). We hypothesized that clin. administered antiarrhythmic drugs alter the expression of CM, and that the repolarization changes characteristic of CM can modulate the effects of antiarrhythmic drugs. We studied conscious, chronically-instrumented dogs paced for two 1-h periods to study the effects of drugs on the evolution of memory (protocol 1) or for 21 days (protocol 2) to observe the effects of steady-state memory on drug actions. Dogs were treated in both settings with quinidine, lidocaine or E4031, in random order, and within therapeutic serum concn. ranges. Pacing, alone, for 2 h significantly prolonged ERP only near the left ventricular pacing site, whereas pacing alone for 21 days prolonged ERP at all sites ($P < 0.05$). Quinidine and E4031, but not lidocaine, prolonged repolarization and ERP and suppressed evolution of CM in protocol 1. However, quinidine's effect in prolonging repolarization was diminished in both protocols, while its effect in prolonging ERP was diminished in the 21-day protocol only. In contrast, the effects of E4031 were additive to those of CM, prolonging repolarization and ERP in both protocols, while lidocaine showed no changes in effect at all. Pacing to induce CM significantly affects ventricular repolarization and refractoriness, and there are interactions between CM, quinidine and E4031. Depending on the specific drug, these interactions have the potential to be anti- or proarrhythmic, and may impact importantly on the clin. efficacy of drugs as well as on electrophysiol. testing of drug actions.

IT 113559-13-0, E4031

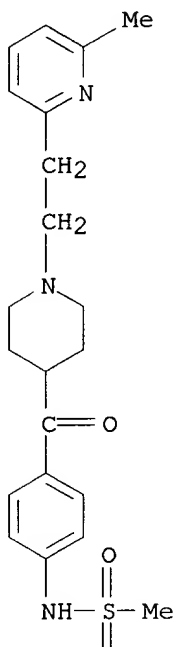
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(interactions between antiarrhythmic drugs and cardiac memory)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 17 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:315373 HCAPLUS
DOCUMENT NUMBER: 135:190122
TITLE: Transgenic mice overexpressing human KvLQT1 dominant-negative isoform. Part II: Pharmacological profile
AUTHOR(S): Lande, G.; Demolombe, S.; Bammert, A.; Moorman, A.; Charpentier, F.; Escande, D.
CORPORATE SOURCE: Laboratoire de Physiopathologie et de Pharmacologie Cellulaires et Moléculaires G&R Laennec, INSERM U533, Faculté de Médecine, Nantes, 44035, Fr.
SOURCE: Cardiovascular Research (2001), 50(2), 328-334
CODEN: CVREAU; ISSN: 0008-6363

Searched by Thom Larson, STIC, 308-7309

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: The acquired long QT syndrome results most often from the action of IKr blocking-drugs on cardiac repolarization. We have evaluated a transgenic (TG) mouse (FVB) overexpressing a dominant-neg. KvLQT1 isoform, as an in vivo screening model for IKr blocking drugs. Results: In TG mice, six-lead ECGs demonstrated sinus bradycardia, atrioventricular block, and QTc prolongation. Various drugs were injected i.p. after blockade of the autonomic nervous system and serial ECGs were recorded. The end of the initial rapid phase of the T wave cor. for heart rate using a formula for mouse heart (QTrc), was used as a surrogate for the QT interval. Dofetilide, a specific IKr blocker, did not prolong the QTrc interval either in TG or in wild-type (WT) mice but dose-dependently lengthened the sinus period in TG mice but not in WT mice. Other IKr blockers including E 4031, haloperidol, sultopride, astemizole, cisapride and terikalant behaved similarly to dofetilide. Tedisamil, a blocker of the transient outward current, dose-dependently prolonged the QTrc in WT mice but not in TG mice and also reduced the sinus rhythm in both WT and TG mice. Lidocaine dose-dependently shortened the QTrc interval in TG mice and also lengthened the P wave duration. Nicardipine dose-dependently shortened QTrc and also produced sinus arrest in both WT and TG mice. Conclusions: We conclude that KvLQT1-invalidated TG mice discriminates in vivo drugs that blocks IKr from drugs that block the transient outward current, the sodium current or the calcium current.

IT 113559-13-0, E 4031

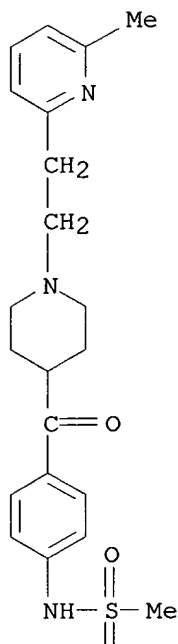
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(transgenic mice overexpressing human KvLQT1 dominant-neg. isoform: pharmacol. profile)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



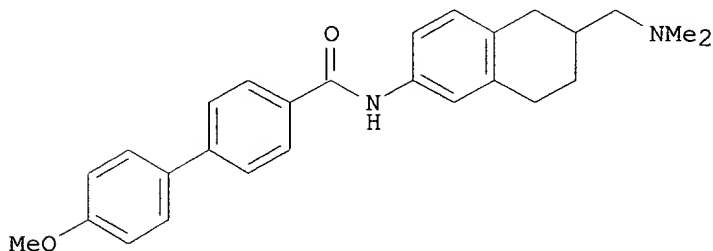
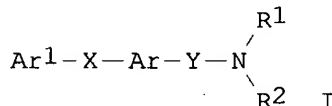
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REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:228848 HCAPLUS
DOCUMENT NUMBER: 134:266103
TITLE: Preparation of N-tetrahydronaphthalenyl carboxamides
as melanin concentrating hormone antagonists
INVENTOR(S): Kato, Kaneyoshi; Terauchi, Jun; Mori, Masaaki; Suzuki,
Nobuhiro; Shimomura, Yukio; Takekawa, Shiro; Ishihara,
Yuji
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 363 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

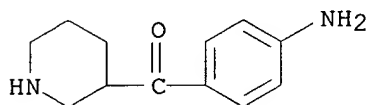
Searched by Thom Larson, STIC, 308-7309

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|-------------------|-----------------|------------|
| WO 2001021577 | A2 | 20010329 | WO 2000-JP6375 | 20000919 |
| WO 2001021577 | A3 | 20011004 | | |
| W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1218336 | A2 | 20020703 | EP 2000-961075 | 20000919 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2002003370 | A2 | 20020109 | JP 2000-290357 | 20000920 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | JP 1999-266298 | A 19990920 |
| | | | JP 1999-357889 | A 19991216 |
| | | | JP 2000-126272 | A 20000420 |
| | | | WO 2000-JP6375 | W 20000919 |
| OTHER SOURCE(S): | | MARPAT 134:266103 | | |
| GI | | | | |



AB The title compds. [I; Ar¹ = (un)substituted cyclic group; X = a spacer having a main chain of 1-6 atoms; Y = a bond, a spacer having a main chain of 1-6 atoms; Ar = (un)substituted monocyclic arom. ring which may be condensed with a 4-8 membered non-arom. ring; R¹, R² = H, a hydrocarbon group which may have substituents; NR¹R² may form a (un)substituted nitrogen-contg. hetero ring; R² may form a spiro ring together with Ar; R², together with the adjacent nitrogen atom and Y, may form a (un)substituted nitrogen-contg. hetero ring] and their salts, useful as agents for preventing or treating obesity, were prepd. and formulated. Thus, reacting 6-amino-2-[(dimethylamino)methyl]tetralin with 4-(4-methoxyphenyl)benzoic acid in the presence of HOBt, WSCD, Et₃N and DMAP in DMF afforded the carboxamide II which showed IC₅₀ of 40 nM in

GTPgS binding assay.
IT **331759-56-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(prepn. of N-tetrahydronaphthalenyl carboxamides as melanin concg.
hormone antagonists)
RN 331759-56-9 HCAPLUS
CN Methanone, (4-aminophenyl)-3-piperidinyl- (9CI) (CA INDEX NAME)



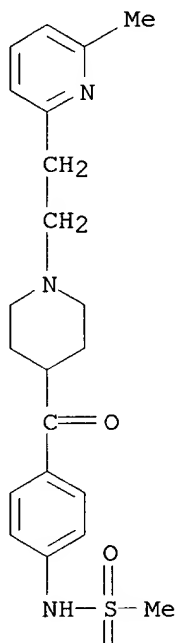
L14 ANSWER 19 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:114132 HCAPLUS
DOCUMENT NUMBER: 134:293811
TITLE: Differences in action potential and early
afterdepolarization properties in LQT2 and LQT3 models
of long QT syndrome
AUTHOR(S): Studenik, Christian R.; Zhou, Zhengfeng; January,
Craig T.
CORPORATE SOURCE: Institute of Pharmacology and Toxicology, University
of Vienna, Vienna, Austria
SOURCE: British Journal of Pharmacology (2001), 132(1), 85-92
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 Long QT syndrome has many causes from both acquired and congenital
disorders. For the congenital disorders, their presentation and disease
course are not identical. We studied two pharmacol. models of long QT
syndrome (LQT) to identify differences in cellular electrophysiol.
properties that may account for this. LQT2 was simulated by suppression
of the rapidly activating delayed rectifier potassium current (IKr) with
the drug E-4031, and LQT3 was simulated by slowing of the sodium current
(INa) decay with the toxin ATX II. 2 Single rabbit ventricular cell
action potentials were studied using the amphotericin B perforated patch
clamp technique. Action potential and early afterdepolarization (EAD)
properties were rigorously defined by the frequency power spectra obtained
with fast Fourier transforms. 3 The E-4031 (n = 43 myocytes) and ATX II
(n = 50 myocytes) models produced different effects on action potential
and EAD properties. The major differences are that ATX II, compared with
E-4031, caused greater action potential prolongation, more pos. plateau
voltages, lower amplitude EADs with less neg. take-off potentials, greater
time to the EAD peak voltage, and longer duration EADs. Despite causing
greater action potential prolongation, the incidence of EAD induction was
much less with the ATX II model (28%) than with the E-4031 model (84%).
Thus these two pharmacol. models have strikingly different cellular
electrophysiol. properties. 4 Our findings provide cellular mechanisms
that may account for some differences in the clin. presentation of LQT2
and LQT3.
IT **113559-13-0, E-4031**
RL: ADV (Adverse effect, including toxicity); BUU (Biological use,
unclassified); BIOL (Biological study); USES (Uses)

(calcium, sodium, and potassium channels inhibitors ATX II and E-4031 in LQT2 and LQT3 rabbit models of long QT syndrome and their differences in action potential and early afterdepolarization properties)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 20 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63973 HCAPLUS

DOCUMENT NUMBER: 134:115860

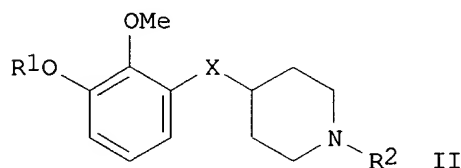
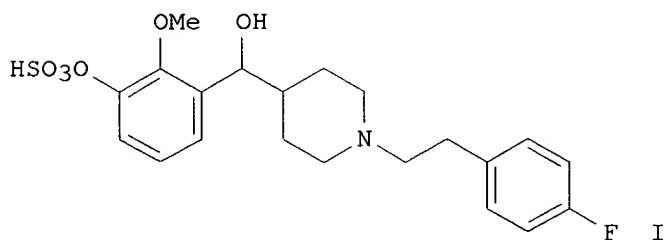
TITLE: Preparation of sulfuric acid mono-[3-({1-[2-(4-fluorophenyl)-ethyl]-piperidin-4-yl}-hydroxy-methyl)-2-methoxy-phenyl]ester and analogs for use as serotonin 5HT2A receptor antagonists

INVENTOR(S): Bernotas, Ronald; Brown, Paul; Emmons, Gary; King,

Searched by Thom Larson, STIC, 308-7309

Chi-Hsin
 PATENT ASSIGNEE(S): Aventis Pharmaceuticals Inc., USA
 SOURCE: PCT Int. Appl., 54 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001005764 | A2 | 20010125 | WO 2000-US19065 | 20000713 |
| WO 2001005764 | A3 | 20011004 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG BR 2000012477 A 20020402 BR 2000-12477 20000713 EP 1202967 A2 20020508 EP 2000-947304 20000713 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL NO 2002000213 A 20020222 NO 2002-213 20020115 PRIORITY APPLN. INFO.: US 1999-354704 A2 19990716 WO 2000-US19065 W 20000713 OTHER SOURCE(S): MARPAT 134:115860 GI | | | | |



AB Prepn. of the title compd. I and its analogs II (R1 = H, trialkylsilane, alkylcarboxy; R2 = (un)substituted arylalkyl, COOR3, H; R3 = alkyl, aryl

or arylalkyl; X = CO or CHOR₄; R₄ = H or alkylcarboxy) is disclosed. Thus, compd. I was prepd. by combined sulfonation/deacetylation of acetic acid {1-[2-(4-fluorophenyl)-ethyl]-piperidin-4-yl}-(3-hydroxy-2-methoxyphenyl)methyl ester. I is an active metabolite of II (R₁ = Me; X = CHOH; R₂ = 4-FC₆H₄CH₂CH₂) and a method for its prepn. and isolation via metab. is claimed. The title compds. are claimed as serotonin 5HT_{2A} receptor antagonists and as such are useful for the treatment of a no. of disease states, e.g. schizophrenia, anxiety, variant angina, anorexia nervosa, cardiac arrhythmias, etc.

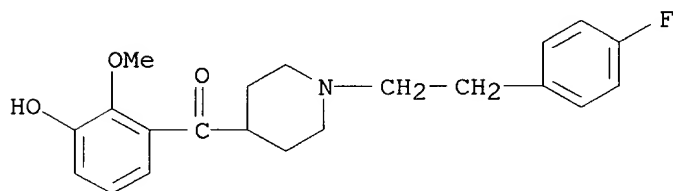
IT **321547-53-9P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of fluorophenylethylpiperidine derivs. as serotonin 5HT_{2A} receptor antagonists)

RN 321547-53-9 HCAPLUS

CN Methanone, [1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl] (3-hydroxy-2-methoxyphenyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 21 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:697933 HCAPLUS

DOCUMENT NUMBER: 134:220696

TITLE: Electropharmacological characterization of cardiac repolarization in German shepherd dogs with an inherited syndrome of sudden death: Abnormal response to potassium channel blockers

AUTHOR(S): Merot, Jocelyn; Probst, Vincent; Debailleul, Michele; Gerlach, Uwe; Moise, N. Sydney; Le Marec, Herve; Charpentier, Flavien

CORPORATE SOURCE: Physiopathologie & Pharmacologie Cellulaires & Moleculaires, Nantes, Fr.

SOURCE: Journal of the American College of Cardiology (2000), 36(3), 939-947

CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study sought to det. whether abnormal ventricular repolarization is implicated in cardiac arrhythmias of German shepherd dogs with inherited sudden death. Moise et al. (9) have identified German shepherd dogs that display pause-dependent lethal ventricular arrhythmias. Ventricular repolarization was studied both in vivo using ECG recordings on conscious dogs and in vitro with a std. microelectrode technique performed on endomyocardial biopsies and Purkinje fibers. Pharmacol. manipulation was used to evaluate the role of potassium channels. In control conditions, ECG parameters were similar in both groups of dogs, except for the PR

interval (18% longer in affected dogs, $p < 0.05$). Injection of d,l-sotalol (2 mg/kg) prolonged QT interval more in affected dogs (+14%, $n = 9$) than it did in unaffected dogs (+6%, $n = 6$, $p < 0.05$) and increased the severity of arrhythmias in affected dogs. In vitro, in control conditions, action potential duration (APD90) of endomyocardial biopsies and Purkinje fibers were significantly longer in affected dogs (resp. $209. \pm .3$ ms, $n = 30$ and $352. \pm .15$ ms, $n = 17$) than they were in unaffected dogs ($197. \pm .4$ ms, $n = 25$ and $300. \pm .9$ ms, $n = 30$) at a pacing cycle length (PCL) of 1,000 ms. This difference increased with PCL. The kinetics of adaptation of APD90 to a change in PCL was faster in affected dogs. D,l-sotalol (10-5 and 10-4M) increased APD90 in both groups of dogs, but this increase was greater in affected dogs, with the occurrence of triggered activity on Purkinje fibers. E-4031 (10-7 and 10-6 M), an IKr-blocker, increased APD90 similarly in both groups of dogs. Chromanol 293B (10-6 and 10-5M), an IKs-blocker, increased significantly APD90 in unaffected dogs but had no effect in affected dogs. These results support the hypothesis of an abnormal cardiac repolarization in affected dogs. The effects of 293B suggest that IKs may be involved in this anomaly.

IT **113559-13-0**, E-4031

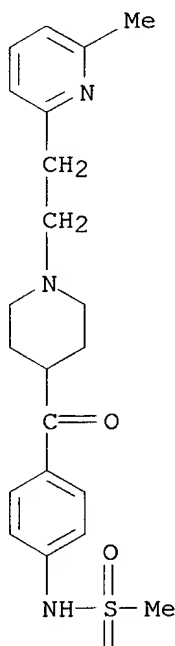
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(cardiac repolarization in dogs with inherited sudden death syndrome)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

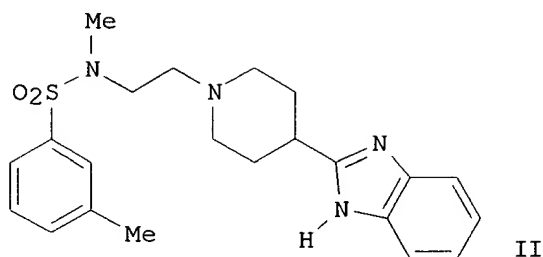
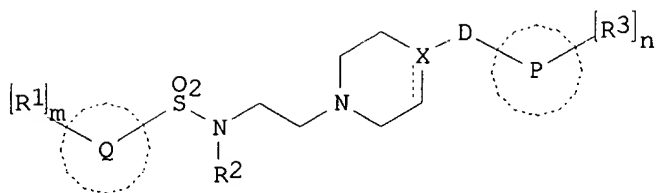
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REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:688218 HCAPLUS
 DOCUMENT NUMBER: 133:252456
 TITLE: Preparation of N-[2-piperazino(or piperidino)ethyl] benzenesulfonamides and thiophenesulfonamides as 5-HT7 receptor antagonists
 INVENTOR(S): Lovell, Peter John
 PATENT ASSIGNEE(S): Smithkline Beecham Plc, UK
 SOURCE: PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|--|-----------------|------------|
| ----- | ---- | ----- | ----- | ----- |
| WO 2000056712 | A1 | 20000928 | WO 2000-EP2267 | 20000314 |
| W: | | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | |
| RW: | | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | |
| EP 1163221 | A1 | 20011219 | EP 2000-916945 | 20000314 |
| R: | | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | |
| PRIORITY APPLN. INFO.: | | | GB 1999-6624 | A 19990323 |
| | | | WO 2000-EP2267 | W 20000314 |
| OTHER SOURCE(S): | | MARPAT 133:252456 | | |
| GI | | | | |



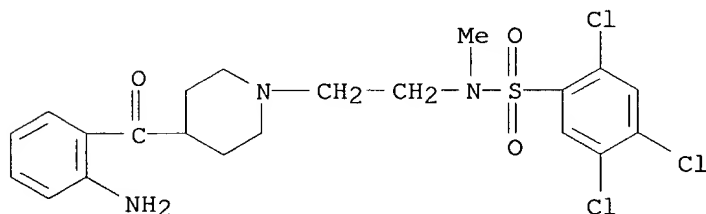
AB The title compds. [I; Q = Ph, thienyl; R1 = halo, OH, alkyl, etc.; m = 0-3; R2 = alkyl; X = N, C, CH; D = a single bond; CO, O, CH2 subject to the proviso that when X = N then D is not O; P = Ph, naphthyl, 5-6 membered heteroaryl contg. 1-3 heteroatoms selected from O, N and S, etc.; R3 = (un)substituted alkyl; n = 0-3] having 5-HT7 receptor antagonist activity, and therefore useful in the treatment of CNS and other disorders, were prep'd. E.g., a multi-step synthesis of benzenesulfonamide II was given. All compds. I tested had a pKi of 6.2-9.0 against 5-HT7 receptor binding.

IT **295790-09-9P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-[2-piperazino(or piperidino)ethyl] benzenesulfonamides and thiophenesulfonamides as 5-HT7 receptor antagonists)

RN 295790-09-9 HCAPLUS

CN Benzenesulfonamide, N-[2-[4-(2-aminobenzoyl)-1-piperidinyl]ethyl]-2,4,5-trichloro-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

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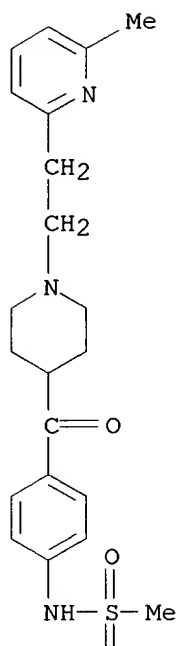
THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 23 OF 193 HCAPLUS COPYRIGHT 2002 ACS

Searched by Thom Larson, STIC, 308-7309

ACCESSION NUMBER: 2000:675819 HCAPLUS
DOCUMENT NUMBER: 134:141545
TITLE: Influence of the antiarrhythmic agent E-4031 on
Na⁺/Ca²⁺ exchange by the protein kinase C pathway in
guinea pig ventricular myocytes
AUTHOR(S): Wu, Dong-Mei; Lu, Ji-Yuan; Wu, Bo-Wei
CORPORATE SOURCE: Department of Physiology, Shanxi Medical University,
Taiyuan, 030001, Peop. Rep. China
SOURCE: Zhongguo Yaolixue Yu Dulixue Zazhi (2000), 14(4),
253-257
CODEN: ZYYZEW; ISSN: 1000-3002
PUBLISHER: Zhongguo Yaolixue Yu Dulixue Zazhi Biarjibu
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the possible signaling pathways of E-4031 in increasing
Na⁺/Ca²⁺ exchange, the quasi-steady-state current-voltage relationship in
isolated guinea pig ventricular myocytes was measured by whole-cell
voltage-clamp techniques with a ramp pulse protocol. At +50 mV,
12-O-tetradecanoylphorbol 13-acetate (TPA), a protein kinase C activator,
at 5, 10, and 15 nM increased the Ni²⁺-sensitive current by 116%, 225%,
and 289%, resp. Tamoxifen, a selective antagonist of protein kinase C, at
20 .mu.M completely prevented the current changes induced by E-4031 and
TPA. The results suggest that E-4031 stimulates Na⁺/Ca²⁺ exchange via a
protein kinase C-dependent pathway.
IT 113559-13-0, E 4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(antiarrhythmic agent E-4031 effects on sodium/calcium exchange by the
protein kinase C pathway in ventricular myocytes)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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PAGE 2-A



● 2 HCl

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 24 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:415733 HCAPLUS
 DOCUMENT NUMBER: 133:246973
 TITLE: Effect of E-4031 on Na⁺/Ca²⁺ exchange current in cardiac myocytes
 AUTHOR(S): Li, Jiangguo; Wu, Bowei; Wen, Dun
 CORPORATE SOURCE: Dept. of Physiology, Shanxi Medical University, Taiyuan, 030001, Peop. Rep. China
 SOURCE: Shanxi Yike Daxue Xuebao (2000), 31(1), 3-5
 CODEN: SDXYF5; ISSN: 1007-6611
 PUBLISHER: Shanxi Yike Daxue Xuebao Bianjishi
 DOCUMENT TYPE: Journal
 LANGUAGE: Chinese
 AB The effects of E-4031 on the Na⁺/Ca²⁺ exchange current were studied in guinea pig ventricular myocytes using whole-cell voltage-clamp techniques with a ramp pulse protocol. The current increased (11.±.6)%, (59.±.13)%

Searched by Thom Larson, STIC, 308-7309

and (112. \pm .25)% in cells perfused with 0.01, 0.1 and 1.0 μ M/L E-4031, resp. ($P < 0.05$); results indicate that the concn.-dependent stimulating effects of E-4031 on $\text{Na}^+/\text{Ca}^{2+}$ exchange current may be an important mechanism underling the pos. inotropic action of this new class III antiarrhythmic drug.

IT **113559-13-0**, E-4031

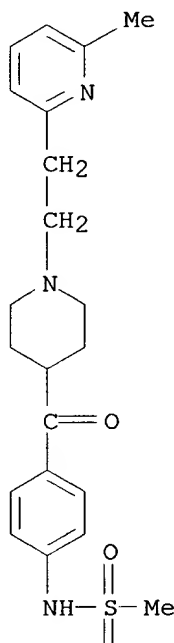
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of E-4031 on $\text{Na}^+/\text{Ca}^{2+}$ exchange current in cardiac myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 25 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:389966 HCAPLUS
 DOCUMENT NUMBER: 133:261314
 TITLE: Enhancement of delayed afterdepolarizations and

Searched by Thom Larson, STIC, 308-7309

triggered activity by class III antiarrhythmic drugs:
multiple effects of E-4031 and dofetilide

AUTHOR(S): Xie, J-T.; Yuan, C-S.; Zhou, Z.; January, C. T.
CORPORATE SOURCE: Tang Center for Herbal Medicine Research and The
Department of Anesthesia and Critical Care. The
Pritzker School of Medicine, The University of
Chicago, Chicago, IL, USA

SOURCE: Methods and Findings in Experimental and Clinical
Pharmacology (2000), 22(2), 67-76
CODEN: MFEPDX; ISSN: 0379-0355

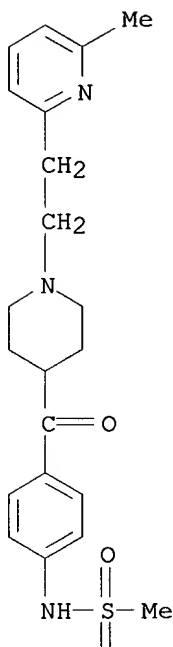
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of class III antiarrhythmic agents E-4031 and dofetilide were
studied on action potentials and subthreshold delayed afterdepolarizations
(DADs) induced by the cardiac glycoside acetylstrophanthidin (AS) in
isolated cardiac Purkinje fibers. Action potentials were recorded from
cardiac Purkinje fibers using microelectrode techniques. E-4031 and
dofetilide consistently increased DAD amplitude, occasionally caused
triggered action potentials and shortened action potential duration. The
application of E-4031 without prior AS exposure, resulted in the typical
class III antiarrhythmic effects of action potential lengthening and the
induction of early afterdepolarizations. These findings suggest that
under our conditions of AS-induced cell Ca²⁺ overload, the effects of the
"pure" class III antiarrhythmic drugs, E-4031 and dofetilide, are markedly
different from those found in non-Ca²⁺ loaded cells. This may represent
an addnl. electrophysiol. mechanism for class III antiarrhythmic drug
toxicity.

IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(enhancement of delayed afterdepolarizations and triggered activity by
class III antiarrhythmic drugs and multiple effects of E-4031 and
dofetilide)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:365375 HCAPLUS
DOCUMENT NUMBER: 133:99094
TITLE: Salutary antiarrhythmic effect of combining a K channel blocker and a .beta.-blocker in a canine model of 7-day-old myocardial infarction
AUTHOR(S): Takatsuki, Seiji; Mitamura, Hideo; Kanki, Hideaki; Sueyoshi, Koichiro; Ogawa, Satoshi
CORPORATE SOURCE: Cardiology Division, Department of Medicine, School of Medicine, Keio University, Tokyo, 160-8582, Japan
SOURCE: Journal of Cardiovascular Pharmacology (2000), 35(6), 914-918
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

AB We sought to examine whether the antiarrhythmic effect of E4031 (E), or IKr channel blocker, is affected by .beta.-adrenergic stimulation using isoproterenol (Iso) or by .beta.-adrenergic blockade (.beta.B) using, ONO1101, in a canine myocardial infarction model. Electrophysiol. studies were performed in 10 dogs with 7-day-old myocardial infarctions. Local QT intervals were measured at 47 sites on the infarcted myocardium using a mapping electrode. QT dispersion (QTd), as defined by the coeff. of variation of QT intervals, was obtained. Inducibility of ventricular arrhythmias was examd. by programmed stimulation. These procedures were repeated during administration of E, E + Iso, and E + .beta.B. The effect of prolonging local QT intervals by E was counteracted by Iso, and was accentuated by .beta.B. The amt. of prolongation was dependent on the baseline QT intervals, and QTd showed a tendency to decrease with E, to increase with E + Iso, and significantly decreased with E + .beta.B. Ventricular tachyarrhythmias were induced in a half of dogs with E + Iso, but were not induced with E + .beta.B. In the presence of adrenergic activation, IKr blockers may exhibit a decreased antiarrhythmic effect. Beneficial synergism can be expected when an IKr blocker is combined with a .beta.-blocker in the subacute phase of myocardial infarction.

IT 113559-13-0, E4031

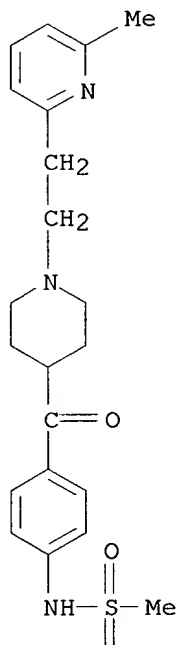
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(antiarrhythmic effect of combining a K channel blocker and a .beta.-blocker in a canine model of myocardial infarction)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

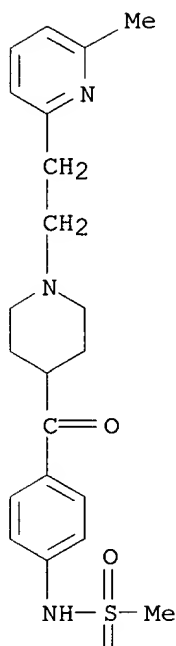
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● 2 HCl

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 27 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:190396 HCAPLUS
DOCUMENT NUMBER: 132:317804
TITLE: Class III anti-arrhythmia drug E-4031 potentiates
Na⁺/Ca²⁺ exchange current in rat ventricular myocytes
AUTHOR(S): Wu, Dong-Mei; Lu, Ji-Yuan; Wu, Bo-Wei
CORPORATE SOURCE: Department of Physiology, Shanxi Medical University,
Tai-yuan, 030001, Peop. Rep. China
SOURCE: Acta Pharmacologica Sinica (2000), 21(3), 249-252
CODEN: APSCG5
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB AIM: To study the effects of E-4031 on the Na⁺/Ca²⁺ exchange currents
(I_{Na/Ca}). METHODS: The quasisteady state current-voltage relationship
from the isolated rat ventricular myocytes was measured using whole-cell
voltage-clamp techniques with a ramp pulse protocol. RESULTS: At
potential of + 50 mV, E-4031 5, 10, and 20 .mu.mol.cntdot.L-1 increased
Ni²⁺ -sensitive current from (0.48.+-.0.12), to (0.78.+-.0.20),
(0.96.+-.0.16), and (1.15.+-.0.13) pA/pF, resp.; tetradecanoylphorbol
acetate (TPA) 50 nmol.cntdot.L-1 increased Ni²⁺ -sensitive current from
(0.60.+-.0.16) to (1.33.+-.0.25) pA/pF. Tamoxifen 20 .mu.mol.cntdot.L-1
completely prevented the current changes induced by E-4031 and TPA.
CONCLUSION: E-4031 stimulates the Na⁺/Ca²⁺ exchange via a protein kinase
C-dependent pathway.
IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(class III anti-arrhythmia drug E-4031 potentiates sodium/calcium
exchange current in rat ventricular myocytes via protein kinase
C-dependent pathway)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

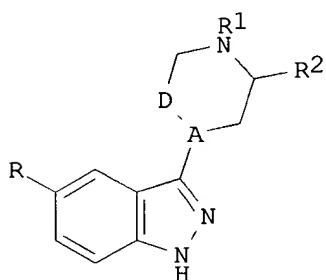
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:98104 HCAPLUS
DOCUMENT NUMBER: 132:151815
TITLE: Preparation of indazoles as 5-HT1F agonists.
INVENTOR(S): Krushinski, Joseph Herman, Jr.; Schaus, John Mehnert
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| EP 978514 | A1 | 20000209 | EP 1999-305915 | 19990726 |

Searched by Thom Larson, STIC, 308-7309

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 US 6133290 A 20001017 US 1999-334157 19990616
 WO 2000006173 A1 20000210 WO 1999-US13834 19990622
 W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD,
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RU, SD,
 SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW,
 AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM,
 GA, GN, GW, ML, MR, NE, SN, TD, TG
 AU 9946961 A1 20000221 AU 1999-46961 19990622
 PRIORITY APPLN. INFO.: US 1998-94940P P 19980731
 WO 1999-US13834 W 19990622
 OTHER SOURCE(S): MARPAT 132:151815
 GI



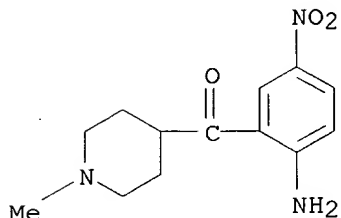
I

AB Title compds. (I; AD = CHCH₂, C:CH; R = NO₂, amino, halo, OH, acylamino; R₁ = H, alkyl, R₂ = H; R₁R₂ = atoms to form a fused 5-7 membered ring), were prepd. as 5-HT_{1F} agonists (no data). Thus, 4-(2-amino-5-nitrobenzoyl)-1-methylpiperidine (prepn. given) in aq. HCl at -5.degree. was treated with aq. NaNO₂; the resulting diazonium salt soln. was added to a -5.degree. soln. of SnCl₂ in aq. HCl followed by 2 h stirring at -3.degree. to give 31.4% 5-nitro-3-(1-methylpiperidin-4-yl)-1H-indazole.

IT **253436-73-6P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of indazoles as 5-HT_{1F} agonists)

RN 253436-73-6 HCAPLUS

CN Methanone, (2-amino-5-nitrophenyl)(1-methyl-4-piperidinyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

5

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

Searched by Thom Larson, STIC, 308-7309

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 29 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:92687 HCAPLUS

DOCUMENT NUMBER: 133:486

TITLE: Potassium channel openers antagonize the effects of class III antiarrhythmic agents in canine Purkinje fiber action potentials: implications for prevention of proarrhythmia induced by class III agents

AUTHOR(S): Kondo, Masahiko; Tsutsumi, Takeshi; Mashima, Saburo
CORPORATE SOURCE: Division of Cardiology, Showa University Fujigaoka Hospital, Yokohama, JapanSOURCE: Japanese Heart Journal (1999), 40(5), 609-619
CODEN: JHEJAR; ISSN: 0021-4868

PUBLISHER: Japanese Heart Journal Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We studied the effects of potassium channel openers (PCOs) on frequency dependent prolongations of action potential duration (APD), triggered activities and oscillatory action potentials (OSC) induced by E-4031 and dofetilide. The action potentials of canine Purkinje fibers were recorded by a glass microelectrode technique. The effects of E-4031 (10⁻⁶ M) as well as that of addnl. nicorandil (2 .times. 10⁻⁵ M) on the APD were examd. When abnormal automaticity was obsd. under perfusion of E-4031 (10⁻⁵ M) or dofetilide (10⁻⁵ M), action potentials were recorded continuously to est. the sequential effects of addnl. perfusion of nicorandil (6 .times. 10⁻⁵ M) or Y-26763 (10⁻⁵ M) on triggered activities and OSC. APD prolongation by E-4031 at slower stimulation rates (cycle lengths 1000 ms) was suppressed by nicorandil in a dose dependent manner. Both nicorandil and Y-26763 abolished the train of early after-depolarization (EAD) due to E-4031 or dofetilide with a shifting of the resting membrane potential to a more neg. level. PCOs also normalized dofetilide induced abnormal automaticities (EAD, OSC). The antagonistic actions of PCOs on changes in action potential induced by class III antiarrhythmic agents may prevent the development of proarrhythmias produced by these agents.

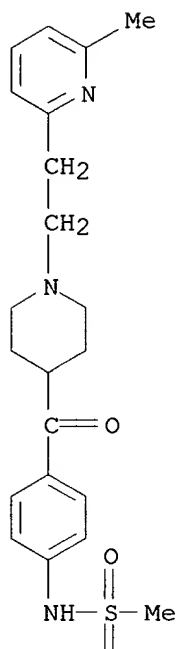
IT 113559-13-0, E-4031

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(potassium channel openers antagonize class III antiarrhythmic drugs
effect in Purkinje fiber action potentials: implications for
proarrhythmia prevention)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

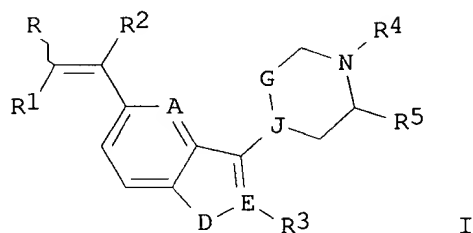
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 30 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:15205 HCAPLUS
 DOCUMENT NUMBER: 132:64178
 TITLE: Preparation of 3-(1-methylpiperidin-4-yl)-1H-indoles as 5-HT_{1F} agonists
 INVENTOR(S): Krushinski, Joseph Herman, Jr.; Rocco, Vincent Patrick; Schaus, John Mehnert
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: PCT Int. Appl., 74 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

Searched by Thom Larson, STIC, 308-7309

 WO 2000000490 A2 20000106 WO 1999-US14502 19990624
 W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
 DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
 JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
 MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
 TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
 MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
 ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
 CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 AU 9949614 A1 20000117 AU 1999-49614 19990624
 PRIORITY APPLN. INFO.: US 1998-90872P P 19980626
 US 1998-94957P P 19980731
 WO 1999-US14502 W 19990624
 OTHER SOURCE(S): MARPAT 132:64178
 GI



AB The title compds. [I; A = N, C; D = O, S, NH; E = C, N; GJ = CH₂CH, CH:C; R = (un)substituted Ph, naphthyl, heteroaryl; R₁, R₂ = H, halo, alkyl, alkoxy; R₃ = H, alkyl; R₄ = H, alkyl; R₅ = H or R₄ and R₅ combine, together with the 6-membered ring to which they are attached, to form a 6:5, 6:6, or 6:7 fused bicyclic ring; provided that: A may be N only when D = NH and E = C; E may be N only when D = NH and A = C; when E = N, R₃ is not a substituent], useful for activating 5-HT_{1F} receptors and inhibiting neuronal protein extravasation in a mammal, and therefore useful in the treatment of migraine and assocd. disorders, were prepd. and formulated. Thus, reacting 5-bromo-3-(1-methylpiperidin-4-yl)-1H-indole with 4-chlorostyrene in the presence of tri-o-tolylphosphine, Pd(OAc)₂ and ET₃N in DMF afforded 53.5% I [D = NH; E = C; A = C; GJ = CH₂CH; R₅ = H; R₄ = Me; R₁ = R₂ = H; R = 4-ClC₆H₄]. Compds. I are effective at 0.1-15 mg/kg/day.

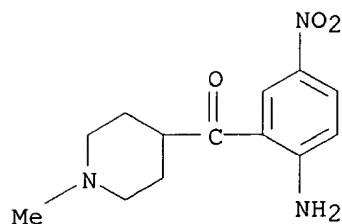
IT **253436-73-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 3-(1-methylpiperidin-4-yl)-1H-indoles as 5-HT_{1F} agonists)

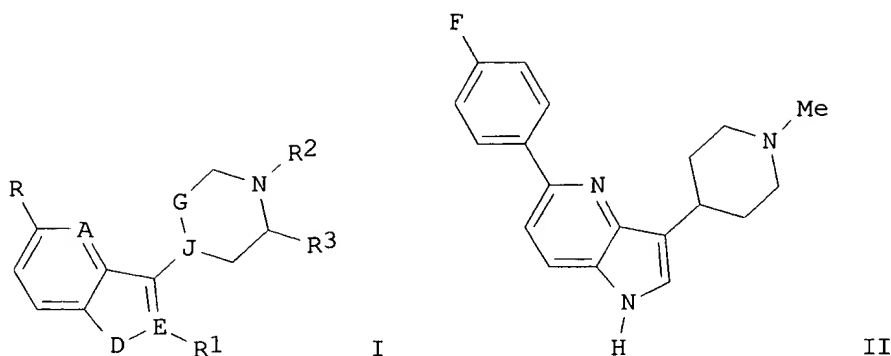
RN 253436-73-6 HCAPLUS

CN Methanone, (2-amino-5-nitrophenyl)(1-methyl-4-piperidinyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 31 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:15199 HCAPLUS
 DOCUMENT NUMBER: 132:64177
 TITLE: Preparation of 3-(1-methylpiperidin-4-yl)-1H-indoles and 3-(1-methylpiperidin-4-yl)-4-aza-1H-indoles as 5-HT1F agonists
 INVENTOR(S): Filla, Sandra Ann; Koch, Daniel James; Mathes, Brian Michael; Rocco, Vincent Patrick
 PATENT ASSIGNEE(S): Eli Lilly and Company, USA
 SOURCE: PCT Int. Appl., 76 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2000000487 | A1 | 20000106 | WO 1999-US14400 | 19990625 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9948318 | A1 | 20000117 | AU 1999-48318 | 19990625 |
| EP 1089993 | A1 | 20010411 | EP 1999-931907 | 19990625 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002519348 | T2 | 20020702 | JP 2000-557248 | 19990625 |
| US 6358972 | B1 | 20020319 | US 2000-701934 | 20001205 |
| PRIORITY APPLN. INFO.: | | | US 1998-91198P | P 19980630 |
| | | | WO 1999-US14400 | W 19990625 |
| OTHER SOURCE(S): | | | MARPAT 132:64177 | |
| GI | | | | |



AB The title compds. [I; A = N, C; D = O, S, NH; E = C, N; GJ = CH₂CH, CH:C; R = (un)substituted Ph, naphthyl, heteroaryl; R₁, R₂ = H, alkyl; R₃ = H or R₂ and R₃ combine, together with the 6-membered ring to which they are attached, to form a 6:5, 6:6, or 6:7 fused bicyclic ring; with the provisos that: A may be N only when D = NH and E = C; E may be N only when D = NH and A = C; E = N, R₁ is not a substituent] which are useful for activating 5-HT_{1F} receptors (no data) and inhibiting neuronal protein extravasation in a mammal, and therefore useful for the treatment of migraine, were prepd. and formulated. Thus, reacting O-trifluoromethanesulfonyl-3-(1-methylpiperidin-4-yl)-5-hydroxy-4-aza-1H-indole with 4-fluorophenylboronic acid in the presence of Pd(PPh₃)₄ and aq. NaHCO₃ in THF afforded 79% the title compd. II. Compds. I are effective at 0.1-15 mg/kg/day.

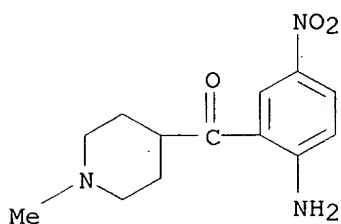
IT **253436-73-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 3-(1-methylpiperidin-4-yl)-1H-indoles and 3-(1-methylpiperidin-4-yl)-4-aza-1H-indoles as 5-HT_{1F} agonists)

RN 253436-73-6 HCAPLUS

CN Methanone, (2-amino-5-nitrophenyl)(1-methyl-4-piperidinyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 32 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:795686 HCAPLUS

DOCUMENT NUMBER: 132:35505

TITLE: Novel multibinding potassium channel drugs and their uses

INVENTOR(S): Jacobsen, John R.; Eastman, Donna; Griffin, John H.

Searched by Thom Larson, STIC, 308-7309

PATENT ASSIGNEE(S): Advanced Medicine, Inc., USA
 SOURCE: PCT Int. Appl., 175 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 25
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|--|----------|-----------------|----------|
| WO 9964050 | A1 | 19991216 | WO 1999-US12777 | 19990607 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2318745 | AA | 19991216 | CA 1999-2318745 | 19990607 |
| CA 2318806 | AA | 19991216 | CA 1999-2318806 | 19990607 |
| CA 2319142 | AA | 19991216 | CA 1999-2319142 | 19990607 |
| CA 2319153 | AA | 19991216 | CA 1999-2319153 | 19990607 |
| WO 9963984 | A1 | 19991216 | WO 1999-US11801 | 19990607 |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| WO 9963932 | A2 | 19991216 | WO 1999-US12724 | 19990607 |
| WO 9963932 | A3 | 20000203 | | |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| WO 9964045 | A1 | 19991216 | WO 1999-US12754 | 19990607 |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
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| AU 9944264 | A1 | 19991230 | AU 1999-44264 | 19990607 |
| AU 9945511 | A1 | 19991230 | AU 1999-45511 | 19990607 |
| AU 9946726 | A | 19991230 | AU 1999-46726 | 19990607 |

EP 1086063 A1 20010328 EP 1999-927330 19990607
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

EP 1085879 A2 20010328 EP 1999-928442 19990607
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

EP 1085890 A1 20010328 EP 1999-930122 19990607
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

EP 1089749 A1 20010411 EP 1999-928447 19990607
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2002517437 T2 20020618 JP 2000-553053 19990607
 JP 2002517466 T2 20020618 JP 2000-553118 19990607

PRIORITY APPLN. INFO.:
 US 1998-88465P P 19980608
 US 1998-93068P P 19980716
 US 1998-113864P P 19981224
 WO 1999-US11801 W 19990607
 WO 1999-US12724 W 19990607
 WO 1999-US12754 W 19990607
 WO 1999-US12777 W 19990607

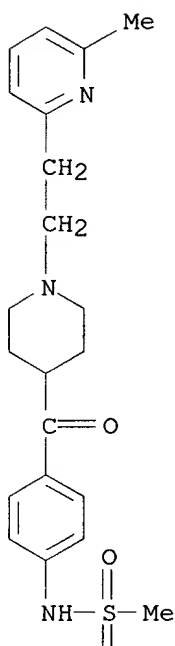
AB This invention relates to novel multibinding compds., LpXq [where L = a ligand capable of binding to a K⁺ channel; X = a linker; p = 2-10; q = 1-20], that bind to potassium (K⁺) channels and modulate their activity. Combinatorial arrays, methods of synthesis, and methods of assaying the dimeric and multimeric compds. are also embodied by the invention. A no. of divalent prophetic examples for compds. contg. two aryl ligands and a difunctional linker are given. Compds. of this invention are useful in the treatment of diseases and conditions of mammals that are mediated by K⁺ channels, such as diabetes, hypertension, and arrhythmia (no data). The claimed multibinding compds., which combine a K⁺ channel opener with little or no effect on cardiac action potential and a Class III antiarrhythmic compd., provide greater biol. and/or therapeutic effects than the aggregate of the unlinked ligands due to their multibinding properties (no data). Ligands may include quinidine, glibenclamide, procaine, tetra-Et ammonium, clofilium, melperone, pinacidil, WAY-123398, cromakalim, propofol, thiopentone, risotilide, almokalant, bretylium, N-acetylprocainamide, tacrine, UK66914, RP58866, 4-aminopyridine, RP49356, alinidine, chromanol 293B, L-768673 and its analogs, bethanidine, disopyramide, desethylamiodarone, NE-10064, artilide, dofetilide, E-4031, sematilide, ambasilide, azimilide, tedisamil, dronedarone, ibutilide, sotalol, benzodiazepine analogs, and amiodarone.

IT **113559-13-ODP**, E-4031, dimeric and multimeric derivs. of
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (target compd.; prepn. of multibinding K⁺ channel drugs as antidiabetics, antihypertensives, and antiarrhythmics)

RN **113559-13-0** HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 33 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:716937 HCAPLUS
DOCUMENT NUMBER: 132:30556
TITLE: Correction of defective protein trafficking of a mutant HERG potassium channel in human long QT syndrome. Pharmacological and temperature effects
AUTHOR(S): Zhou, Zhengfeng; Gong, Qiuming; January, Craig T.
CORPORATE SOURCE: Section of Cardiology, Department of Medicine and Physiology, University of Wisconsin, Madison, WI, 53792, USA
SOURCE: Journal of Biological Chemistry (1999), 274(44), 31123-31126
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English

AB The chromosome 7-linked form of congenital long QT syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (HERG) that encodes the rapidly activating delayed rectifier potassium channel. One mechanism for the loss of normal channel function in LQT2 is defective protein trafficking, which results in the failure of the channel protein to reach the plasma membrane. Here we show that the N470D LQT2 mutant protein is trafficking-deficient when expressed at 37.degree.C in HEK293 cells, whereas at 27.degree.C its trafficking to the plasma membrane and channel function are markedly improved. We further show that the antiarrhythmic drug E-4031, which selectively blocks HERG channels, also corrects defective protein trafficking of the N470D mutant and can restore the generation of HERG current. Similar findings were obtained with the drugs astemizole and cisapride, as well as with high concns. of glycerol. The effect of E-4031 on HERG protein trafficking was concn.-dependent and required low drug concns. (satn. present at 5 .mu.M), developed rapidly with drug exposure, and occurred post-translationally. These findings suggest that protein misfolding leading to defective trafficking of some HERG LQT mutations may be cor. by specific pharmacol. strategies.

IT 113559-13-0, E-4031

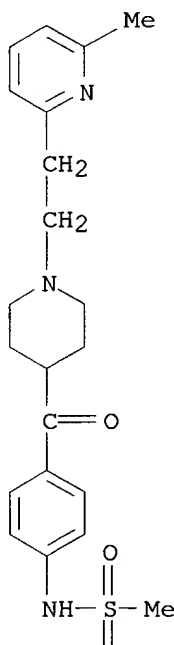
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(E-4031 corrects defective protein trafficking and restores generation of cardiac HERG current)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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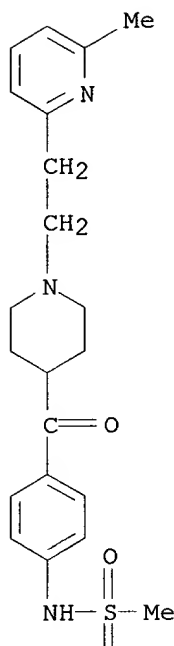
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REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 34 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:609773 HCAPLUS
DOCUMENT NUMBER: 132:132045
TITLE: Effect of antiarrhythmic drug E-4031 on Na⁺/Ca²⁺
exchange currents in isolated guinea pig ventricular
myocytes
AUTHOR(S): Wu, Dong-Mei; Lu, Ji-Yuan; Bian, Zhu-Ping; Dun, Wen;
Wu, Bo-Wei
CORPORATE SOURCE: Department of Physiology, Shanxi Medical University,
Taiyuan, 030001, Peop. Rep. China
SOURCE: Zhongguo Yaolixue Yu Dulixue Zazhi (1999), 13(3),
183-186
CODEN: ZYYZEW; ISSN: 1000-3002
PUBLISHER: Zhongguo Yaolixue Yu Dulixue Zazhi Biarjibu
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to study the effect of E-4031 on Na⁺/Ca²⁺ exchange, the
quasi-steady state current-voltage relationship from the isolated guinea
pig ventricular myocytes was measured using whole-cell voltage-clamp
techniques with a ramp pulse protocol. The results showed that at
membrane potential of +50 mV and -100 mV, E-4031 0.1, 1, 10, and 50
.mu.mol .cntdot. L-1 increased the Ni²⁺-sensitive current by (70.+-.37)%,
(91.+-.53)%, (118.+-.63)%, (121.+-.51)%, and by (25.+-.20)%, (51.+-.32)%,
(113.+-.84)%, (93.+-.73)%, resp. E-4031 increased the Na⁺/Ca²⁺ exchange
currents, which may be an important mechanism underlying the pos.
inotropic action.
IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(effect of antiarrhythmic drug E-4031 on Na⁺/Ca²⁺ exchange currents in
isolated guinea pig ventricular myocytes)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 35 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1999:476863 HCAPLUS
 DOCUMENT NUMBER: 131:237730
 TITLE: Effects of K⁺ channel modulators on the relationship between action potential duration and Ca²⁺ transients in single ventricular myocytes of the guinea pig
 AUTHOR(S): Tokuno, Tomoaki; Muraki, Katsuhiko; Watanabe, Minoru; Imaizumi, Yuji
 CORPORATE SOURCE: Department of Pharmacology & Therapeutics, Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya, 467-8603, Japan
 SOURCE: Japanese Journal of Pharmacology (1999), 80(3), 243-253
 CODEN: JJPAAZ; ISSN: 0021-5198
 PUBLISHER: Japanese Pharmacological Society
 DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English

AB Effects of K⁺ channel modulators, cromakalim and E4031 [1-[2-(6-methyl-2-pyridyl)-ethyl]-4-(4-methylsulfonylaminobenzoyl) piperidine], on the relation between the action potential duration (APD) and Ca²⁺ transients were examd. in single myocytes isolated from guinea pig cardiac left ventricle. Application of cromakalim decreased APD at 90% repolarization (APD₉₀) and Ca²⁺ transient elicited at 0.5 Hz (IC₅₀s=0.6 and 3 .mu.M, resp.). Application of 0.3 .mu.M E4031 increased these parameters by 110% and 45%, resp. Under voltage-clamp, the relation between the duration of depolarization to 0 mV and Ca²⁺ transients could be described by the sum of two exponential components; the time consts. were approx. 5 and 280 ms, resp. The first component was abolished by 10 .mu.M ryanodine, suggesting the involvement of Ca²⁺-induced Ca²⁺ release (CICR). Neither cromakalim nor E4031 directly affected Ca²⁺ current and Ca²⁺ transients under voltage clamp. When APD was changed by K⁺ channel modulators, the relation between APD₉₀ and Ca²⁺-transients was almost similar to that obtained by changing the depolarization duration under voltage-clamp. CICR was changed significantly only when APD₉₀ was markedly shortened by cromakalim. The extensively prolonged AP and Ca²⁺ transient in the presence of E4031 were reduced by an addn. of cromakalim. It is concluded that these two K⁺ channel modulators can significantly alter the AP-induced Ca²⁺ transient mainly by changing APD, which regulates both Ca²⁺ influx and extrusion.

IT 113559-13-0, E4031

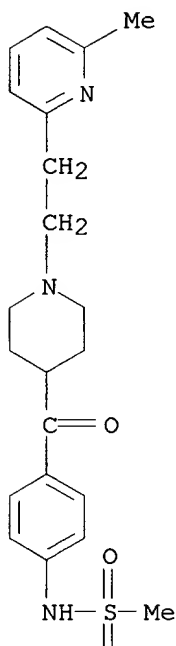
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of K⁺ channel modulators on relationship between action potential duration and Ca²⁺ transients in single ventricular myocytes of guinea pig)

RN 113559-13-0 . HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 36 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1999:405690 HCAPLUS
 DOCUMENT NUMBER: 131:193705
 TITLE: Heterogeneous distribution of the two components of delayed rectifier K⁺ current: a potential mechanism of the proarrhythmic effects of methanesulfonanilideclass III agents
 AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Liu, Weiran; Tsuji, Yukiomi; Toyama, Junji; Kodama, Itsuo
 CORPORATE SOURCE: Research Institute of Environmental Medicine, Division of Regulation of Organ Function, Department of Circulation, Nagoya University, Nagoya, Japan
 SOURCE: Cardiovascular Research (1999), 43(1), 135-147
 CODEN: CVREAU; ISSN: 0008-6363
 PUBLISHER: Elsevier Science B.V.
 DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English

AB Objective: To elucidate the regional difference of the K⁺ current blocking effects of methanesulfonanilide class III agents. Methods: Regional differences in action potential duration (APD) and E-4031-sensitive component (IK_r) as well as -insensitive component (IK_s) of the delayed rectifier K⁺ current (IK) were investigated in enzymically isolated myocytes from apical and basal regions of the rabbit left ventricle using the whole-cell clamp technique. Results: At 1 Hz stimulation, APD was significantly longer in the apex than in the base (223.1 vs. 182.7 ms); application of 1 μ M E-4031 caused more significant APD prolongation in the apex than in the base (32.5% vs. 21.0%), resulting in an augmentation of regional dispersion of APD. In response to a 3-s depolarization pulse to +40 mV from a holding potential of -50 mV, both IK tail and IK_s tail densities were significantly smaller in apical than in basal myocytes (IK: 1.56 vs. 2.09 pA/pF; IK_s: 0.40 vs. 1.43), whereas IK_r tail d. was significantly greater in the apex than in the base (1.15 vs. 0.66 pA/pF). The ratio of IK_s/IK_r for the tail current in the apex was significantly smaller than that in the base (0.51 vs. 3.09). No statistical difference was obsd. in the voltage dependence as well as activation and deactivation kinetics of IK_r and IK_s between the apex and base. Isoproterenol (1 μ M) increased the time-dependent outward current of IK_s by 111% during the 3-s depolarizing step at +40 mV and its tail current by 120% on repolarization to the holding potential of -50 mV, whereas it did not affect IK_r. Conclusions: The regional differences in IK, in particular differences in its two components may underlie the regional disparity in APD, and that methanesulfonanilide class III antiarrhythmic agents such as E-4031 may cause a greater spatial inhomogeneity of ventricular repolarization, leading to re-entrant arrhythmias.

IT **113559-13-0**, E 4031

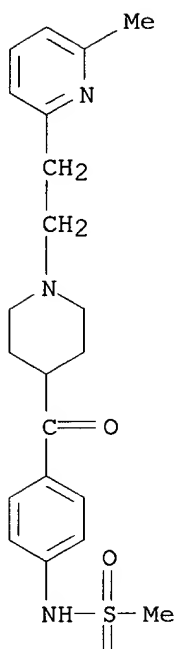
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(heterogeneous distribution of two components of delayed rectifier K⁺ current as potential mechanism of proarrhythmic effects of methanesulfonanilide class III agents such as E 4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 37 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:374481 HCAPLUS
DOCUMENT NUMBER: 131:27360
TITLE: E 4031
AUTHOR(S): Anon.
CORPORATE SOURCE: N. Z.
SOURCE: Drugs in R&D (1999), 1(4), 312-316
CODEN: DRDDFD; ISSN: 1174-5886
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 31 refs., of the pharmacokinetics and pharmacodynamics of E 4031, a potent class III antiarrhythmic agent which selectively blocks the rapidly activating component of the delayed rectifier K⁺ channel current. It may be most useful for the treatment of paroxysmal atrial fibrillation in patients with Wolff-Parkinson-White syndrome and for the prevention of

malignant ventricular arrhythmias and sudden heart arrest.

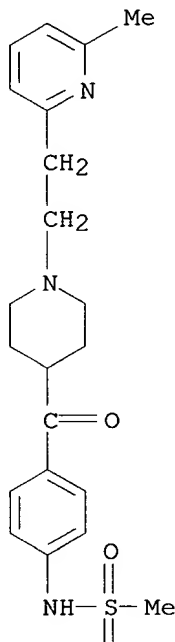
IT 113559-13-0, E 4031

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacol. of E 4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 38 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:335415 HCAPLUS

DOCUMENT NUMBER: 131:111393

TITLE: Effects of verapamil, zatebradine, and E-4031 on the pacemaker location and rate in response to sympathetic

Searched by Thom Larson, STIC, 308-7309

stimulation in dog hearts

AUTHOR(S): Furukawa, Yasuyuki; Miyashita, Yusuke; Nakajima, Koichi; Hirose, Masamichi; Kurogouchi, Fumio; Chiba, Shigetoshi

CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 289(3), 1334-1342
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

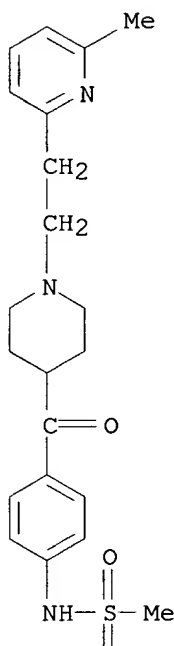
AB To investigate whether slow inward Ca^{2+} current (I_{Ca}), hyperpolarization-activated inward current (I_{f}), and a rapid type of delayed rectifier K^{+} current (I_{Kr}) similarly act on the pacemaker location, sinoatrial node region, and subsidiary superior and inferior pacemaker regions, we studied the effects of verapamil, zatebradine, and E-4031 on the atrial rate and the 3-ms earliest activation region (EAR) detd. from the isochronal activation sequence map in the autonomically decentralized heart of the anesthetized dog. Three blockers decreased atrial rate similarly. Verapamil shifted the EAR from the SA node region to the inferior pacemaker region. The EAR induced by zatebradine was variable, but the EAR induced by E-4031 tended to shift to the inferior pacemaker region. Sympathetic nerve stimulation increased atrial rate and shifted the EAR to the superior pacemaker region. Verapamil attenuated the increased atrial rate by 28%, and it shifted the EAR to the lower pacemaker regions consistently. Zatebradine also attenuated the increased rate by 53% and shifted the EAR from the anterior to the posterior-superior right atrium. E-4031 affected neither the rate nor the EAR in response to sympathetic stimulation. These results suggest that I_{Ca} , I_{f} , and I_{Kr} inhibitors differentially influence the pacemaker activity among three pacemaker regions when sympathetic tone is absent or present and that the role of I_{Ca} , I_{f} , and I_{Kr} of the pacemaker cells distributed in the atrial pacemaker complex is different in the dog heart in situ.

IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of verapamil, zatebradine, and E-4031 on the pacemaker location and rate in response to sympathetic stimulation in dog hearts)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 39 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:239898 HCAPLUS
DOCUMENT NUMBER: 131:82767
TITLE: Intracoronary flecainide induces ST alternans and reentrant arrhythmia on intact canine heart: a role of 4-aminopyridine-sensitive current
AUTHOR(S): Tachibana, Hidetada; Yamaki, Michiyasu; Kubota, Isao; Watanabe, Tetsu; Yamauchi, Sou; Tomoike, Hitonobu
CORPORATE SOURCE: First Department of Internal Medicine, Yamagata University School of Medicine, Yamagata, 990-9585, Japan
SOURCE: Circulation (1999), 99(12), 1637-1643
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

AB The elec. alternans shown on an ST segment, ST alternans, is known as one of the most important predictors of ventricular fibrillation (VF). It has also been reported that sodium channel inhibition changes action potential configuration, esp. on the repolarization phase. Thus, the sodium channel blocker may produce ST alternans and trigger reentrant arrhythmia. A sodium channel blocker (disopyramide, lidocaine, or flecainide) was infused selectively into the left anterior descending coronary artery in anesthetized, open-chest dogs. Sixty unipolar electrograms were simultaneously recorded from the entire cardiac surface of the heart. The amplitude of ST alternans (STa) was detd. as the difference in the ST-segment magnitude between 2 consecutive electrograms. We accepted the greatest STa among 60 leads for evaluation. High-dose flecainide (100 .mu.g .cntdot. kg-1 .cntdot. min-1) increased STa and evoked a spontaneous VF. The STa in high-dose flecainide loading (8.7.+-.3.4 mV; mean.+-.SEM) was significantly greater than that in disopyramide or lidocaine (0.9.+-.0.4 and 0.8.+-.0.2 mV, P<0.05). Treatment of 4-aminopyridine (4-AP) suppressed the increase in STa and the occurrence of VF evoked by flecainide, while E4031 or verapamil did not inhibit those. Flecainide caused the ST alternans that was closely correlated to the occurrence of VF. Because the ST alternans was suppressed by 4-AP treatment, a 4-AP-sensitive current such as Ito or Isus may play an important role on this phenomenon.

IT 113559-13-0, E4031

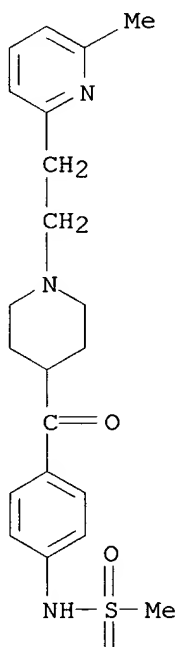
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(intracoronary flecainide induces ST alternans and reentrant arrhythmia on intact canine heart and role of 4-aminopyridine-sensitive current)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 40 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:238023 HCAPLUS
DOCUMENT NUMBER: 131:82763
TITLE: Effects of potassium channel blockers on isolated rat
aorta strip
AUTHOR(S): Chen, Qi; Wang, Xiaoliang
CORPORATE SOURCE: Institute of Materia Medica, Chinese Academy of
Medical Sciences and Peking Union Medical College,
Beijing, 100050, Peop. Rep. China
SOURCE: Yaoxue Xuebao (1999), 34(2), 95-98
CODEN: YHHPAL; ISSN: 0513-4870
PUBLISHER: Yaoxue Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

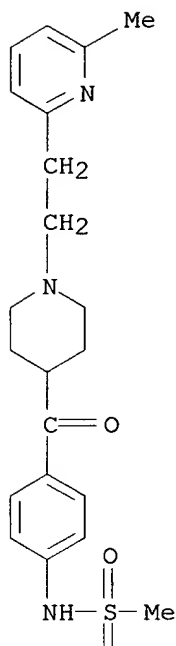
AB The effects of different potassium channel blockers on rat vascular smooth
muscle and the mechanism were studied by using isometric tension recording
of aorta strip. The EC50 values of BaCl2, 4-aminopyridine (4-AP), cesium
chloride (CsCl) and tetraethylammonium (TEA) to increase tension of rat
aorta strips were 0.09.+-.0.08 mmol L-1, 6.43.+-.1.75 mmol L-1,
7.6.+-.1.92 mmol L-1 and 11.5.+-.3.09 mmol L-1, resp. E-4031, sotalol and
glibenclamide did not show any influence on the aorta strip tension. On
the other hand, E-4031, sotalol and 4-AP could inhibit NE-induced
contraction in a dose-dependent manner. E-4031, sotalol and glibenclamide
showed no effect on blood vessel tension at the normal range of concn. and
K+ channel blockers might show different selectivity for heart and blood
vessels.

IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(effects of potassium channel blockers on isolated rat aorta strip)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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L14 ANSWER 41 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:222492 HCAPLUS
DOCUMENT NUMBER: 131:13681
TITLE: Regional differences in effects of E-4031 within the sinoatrial node
AUTHOR(S): Kodama, I.; Boyett, M. R.; Nikmaram, M. R.; Yamamoto, M.; Honjo, H.; Niwa, R.
CORPORATE SOURCE: Research Institute of Environmental Medicine, Nagoya University, Nagoya, 464-01, Japan
SOURCE: American Journal of Physiology (1999), 276(3, Pt. 2), H793-H802
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of block of the rapid delayed rectifier K⁺ current (I_{K,r}) by E-4031 on the elec. activity of small ball-like tissue preps. from different regions of the rabbit sinoatrial node were measured. The

Searched by Thom Larson, STIC, 308-7309

effects of partial block of IK,r by 0.1 .mu.M E-4031 varied in different regions of the node. In tissue from the center of the node, spontaneous activity was generally abolished whereas in tissue from the periphery spontaneous activity persisted, although the action potential was prolonged, the max. diastolic potential was decreased, and the spontaneous activity slowed. After partial block of IK,r, the elec. activity of peripheral tissue was more like that of central tissue under normal conditions. One possible explanation of these findings is that the d. of IK,r is greater in the periphery of the node; this would explain the greater resistance of peripheral tissue to IK,r block and help explain why, under normal conditions, the max. diastolic potential is more neg., the action potential is shorter, and pacemaking is faster in the periphery.

IT **113559-13-0**, E-4031

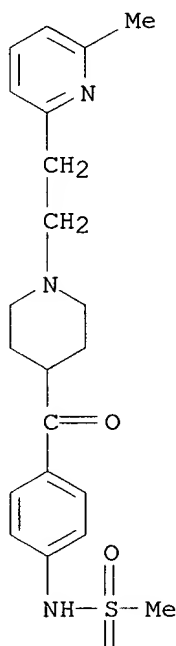
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(regional differences in effects of E-4031 in sinoatrial node)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 42 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:159853 HCAPLUS

DOCUMENT NUMBER: 130:332554

TITLE: Discordant prolongation of the refractory period and repolarization time by a class III agent, E4031, in the healing phase of myocardial infarction

AUTHOR(S): Takatsuki, Seiji; Mitamura, Hideo; Sueyoshi, Koichiro; Kanki, Hideaki; Furuno, Izumi; Ogawa, Satoshi

CORPORATE SOURCE: the Cardiology Division, Department of Medicine, Keio University School of Medicine, Tokyo, 160, Japan

SOURCE: Japanese Heart Journal (1998), 39(5), 687-697

CODEN: JHEJAR; ISSN: 0021-4868

PUBLISHER: Japanese Heart Journal Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Susceptibility to reentrant tachyarrhythmias and the antiarrhythmic efficacy of class III agents are related more to the duration of the refractory period (ERP) than to the repolarization time (RT). We measured both ERP and RT in a canine model of healing myocardial infarction, and evaluated the effect of a class III agent (E4031) on these parameters and on the inducibility of ventricular tachyarrhythmias. ERP and RT on the unipolar electrogram were measured at several cycle lengths in the normal (NZ) and infarct zones (IZ), resp., in 10 canine myocardial infarction models and extra-stimulation was used to induce ventricular arrhythmias. Measurements were repeated after E4031 administration. At baseline, both ERP and RT were significantly longer in IZ than in NZ with ERP/RT ratio also higher in IZ. This ratio tended to increase at longer cycle lengths. E4031 increased ERP and RT both in NZ and IZ at all cycle lengths, but increased the ERP/RT ratio predominantly in IZ. E4031 prevented induction of sustained VT or VF, which was inducible in 3 out of 10 dogs at baseline, although it facilitated induction of VF in 1 dog with no baseline arrhythmia. By increasing the ERP/RT ratio, class III drugs may shorten the relative refractory period in IZ at the expense of a greater ERP difference created between NZ and IZ.

IT 113559-13-0, E4031

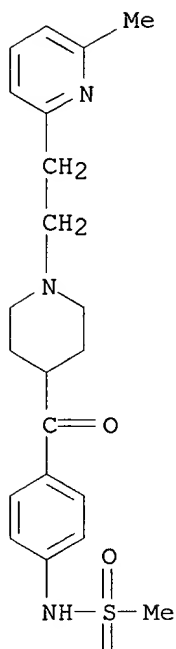
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(prolongation of the refractory period and repolarization time by a class III agent, E4031, in the healing phase of myocardial infarction)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 43 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:19163 HCAPLUS
DOCUMENT NUMBER: 130:204884
TITLE: Effects of low temperature on the chronotropic and inotropic responses to zatebradine, E-4031 and verapamil in isolated perfused dog atria
AUTHOR(S): Kasama, Miho; Furukawa, Yasuyuki; Oguchi, Takeshi; Hoyano, Yuji; Chiba, Shigetoshi
CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, 390-8621, Japan
SOURCE: Japanese Journal of Pharmacology (1998), 78(4), 493-499
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the effects of hypothermia (25.degree.) on the

Searched by Thom Larson, STIC, 308-7309

chronotropic and inotropic effects of zatebradine (a blocker of hyperpolarization-activated inward current, I_f), E-4031 (a blocker of the rapid type of the delayed rectifier K^+ current, I_{Kr}) and verapamil, and on the pos. cardiac responses to isoproterenol after treatment with zatebradine and E-4031 in isolated, blood-perfused dog atria. Hypothermia shifted the dose-response curves to the right for the neg. chronotropic and inotropic effects of verapamil and for the neg. chronotropic and pos. inotropic effects of zatebradine, but not for the neg. chronotropic and pos. inotropic effects of E-4031. Hypothermia attenuated the pos. chronotropic response to isoproterenol or Bay k 8644 (an L type Ca^{2+} channel agonist) and was attenuated more than the inotropic one. Zatebradine selectively inhibited the pos. chronotropic response to isoproterenol at a normal temp., but in hypothermia, it inhibited neither the chronotropic nor inotropic responses. E-4031 did not affect the pos. responses to isoproterenol. These results suggest that verapamil and zatebradine but not E-4031 influence the atrial rate and contractile force much less in hypothermia than in normothermia and that the I_f and inward Ca^{2+} current are sensitive to hypothermia in the heart.

IT **113559-13-0**, E-4031

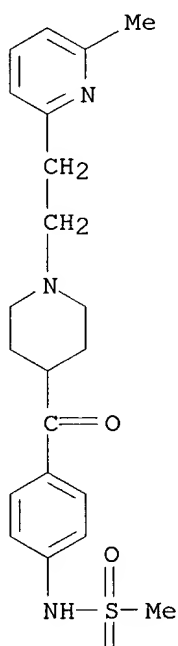
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of low temp. on ch̄ronotropic and inotropic responses to zatebradine, E-4031 and verapamil in isolated perfused dog atria)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 44 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1999:7775 HCAPLUS
 DOCUMENT NUMBER: 130:57225
 TITLE: Device and method for treatment of dysmenorrhea
 INVENTOR(S): Harrison, Donald C.; Liu, James H.; Ritschel, Wolfgang A.; Stern, Roger A.
 PATENT ASSIGNEE(S): UMD, Inc., USA
 SOURCE: PCT Int. Appl., 50 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 9856323 | A1 | 19981217 | WO 1998-US10785 | 19980610 |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | |
| US 6197327 | B1 | 20010306 | US 1998-79897 | 19980515 |
| AU 9876976 | A1 | 19981230 | AU 1998-76976 | 19980610 |
| AU 735407 | B2 | 20010705 | | |
| EP 988009 | A1 | 20000329 | EP 1998-924918 | 19980610 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | |
| BR 9810089 | A | 20000808 | BR 1998-10089 | 19980610 |
| JP 2002515069 | T2 | 20020521 | JP 1999-502556 | 19980610 |
| PRIORITY APPLN. INFO.: | | | US 1997-49325P | P 19970611 |
| | | | US 1998-79897 | A 19980515 |
| | | | WO 1998-US10785 | W 19980610 |

AB Methods, devices, and compns. for treatment of dysmenorrhea comprise an intravaginal drug delivery system contg. an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea. The drug delivery system can be a tampon device, vaginal ring, pessary, tablet, suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream lotion, foam, ointment, paste soln., or gel. The system delivers a higher concn. to the muscle of the uterus, the primary site for the dyskinetic

muscle contraction, which is the pathophysiol. cause of dysmenorrhea. Verapamil vaginal suppositories were prepd. contg. Suppocire AS2, HPMC, and Transcutol.

IT **113559-13-0**, E-4031

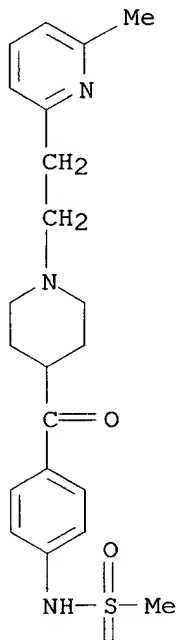
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(vaginal drug delivery devices for treatment of dysmenorrhea)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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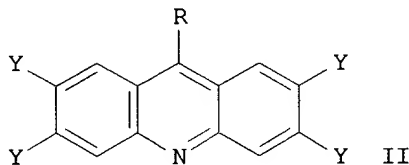
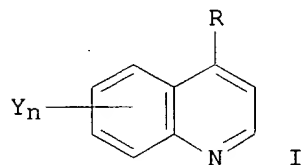
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 45 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1998:794983 HCAPLUS
 DOCUMENT NUMBER: 130:33029
 TITLE: Nitrogen-containing heteroaryl potassium channel blockers for antiarrhythmic agents

Searched by Thom Larson, STIC, 308-7309

INVENTOR(S): Terrar, Derek; Gill, Edward; Mamas, Mamas
 PATENT ASSIGNEE(S): Isis Innovation Limited, UK
 SOURCE: PCT Int. Appl., 23 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|------------------|----------|
| WO 9854148 | A2 | 19981203 | WO 1998-GB1579 | 19980529 |
| WO 9854148 | A3 | 19990304 | | |
| W: JP, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 984941 | A2 | 20000315 | EP 1998-924480 | 19980529 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| PRIORITY APPLN. INFO.: | | | GB 1997-11220 | 19970530 |
| | | | WO 1998-GB1579 | 19980529 |
| OTHER SOURCE(S): | | | MARPAT 130:33029 | |
| GI | | | | |



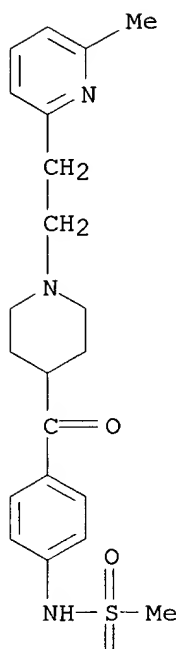
AB Compds. I or II (R = primary or secondary amine or LZ, Y = H, halo, alkyl, alkoxy, perfluoroalkyl, nitro, LZ, n = 1-4, L = linker chain of 1-20 C, N, O, or S; Z = calcium channel blocker) have potassium channel-blocking activity and are useful for the prophylaxis or therapy of arrhythmia.

IT **113559-13-0**, E4031
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (nitrogen-contg. heteroaryl potassium channel blockers for antiarrhythmic agents)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

L14 ANSWER 46 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:755373 HCAPLUS
DOCUMENT NUMBER: 130:133908
TITLE: Comparison of electrophysiologic effects of
intravenous E-4031 and MS-551, novel class III
antiarrhythmic agents, in patients with ventricular
tachyarrhythmias
AUTHOR(S): Naitoh, Naoki; Tagawa, Minoru; Yamaura, Masayuki;
Taneda, Koji; Furushima, Hiroshi; Aizawa, Yoshifusa
CORPORATE SOURCE: First Department of Internal Medicine, Niigata
University School of Medicine, Niigata, Japan
SOURCE: Japanese Heart Journal (1998), 39(4), 457-467
CODEN: JHEJAR; ISSN: 0021-4868
PUBLISHER: Japanese Heart Journal Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Electrophysiol. effects of i.v. E-4031 and MS-551, novel class III
antiarrhythmic agents, were evaluated in 5 and 6 patients with ventricular

Searched by Thom Larson, STIC, 308-7309

tachyarrhythmia, resp. Six patients had sustained ventricular tachycardia (VT) and 5 had ventricular fibrillation (VF). Electrophysiol. study was performed before and after administration of E-4031 and MS-551 [E-4031; loading infusion 9 .mu.g/kg for 5 min + 0.15 .mu.g/kg/min, MS-551; loading infusion 0.3 mg/kg for 5 min + 0.01 mg/kg/min]. The QT intervals were significantly prolonged after administration of E-4031 and MS-551 from 409 .+- . 37 to 455 .+- . 49 ms (11%), and from 359 .+- . 52 to 411 .+- . 63 ms (14%), resp. The QTc intervals were significantly prolonged from 457 .+- . 17 to 494 .+- . 24 ms (8%), and from 410 .+- . 36 to 452 .+- . 47 (10%), resp. There were no significant differences in the QT and QTc intervals between these two agents. The right ventricular effective refractory period (VERP) with E-4031 was prolonged at 600 (from 244 .+- . 27 to 270 .+- . 31 ms, 11 .+- . 2%), 400 (from 222 .+- . 23 to 242 .+- . 24 ms, 9 .+- . 3%), and 300 ms (from 206 .+- . 19 to 218 .+- . 25 ms, 6 .+- . 4%), and those with MS-551 were prolonged at 600 (from 240 .+- . 23 to 268 .+- . 23 ms, 12 .+- . 2%), 400 (from 225 .+- . 22 to 250 .+- . 24 ms, 11 .+- . 4%), and 300 ms (from 213 .+- . 14 to 228 .+- . 18 ms, 7 .+- . 4%). Both E-4031 and MS-551 prolonged VERP in a "reverse" use-dependent manner without changing the conduction velocity. E-4031 prevented the induction of VT in one patient. MS-551 prevented the induction of VT and VF in one patient each. Further evaluation of these selective class III agents may be needed to det. if higher doses are required to achieve the pharmacol. effects in patients with ventricular tachyarrhythmias.

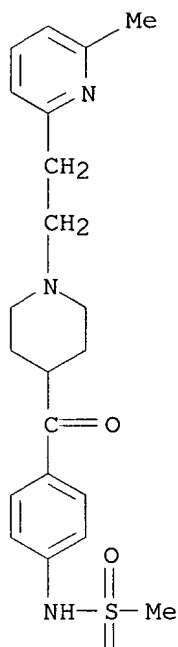
IT 113559-13-0, e-4031

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(comparison of electrophysiol. effects of i.v. E-4031 and MS-551, novel class III antiarrhythmic agents, in patients with ventricular tachyarrhythmias)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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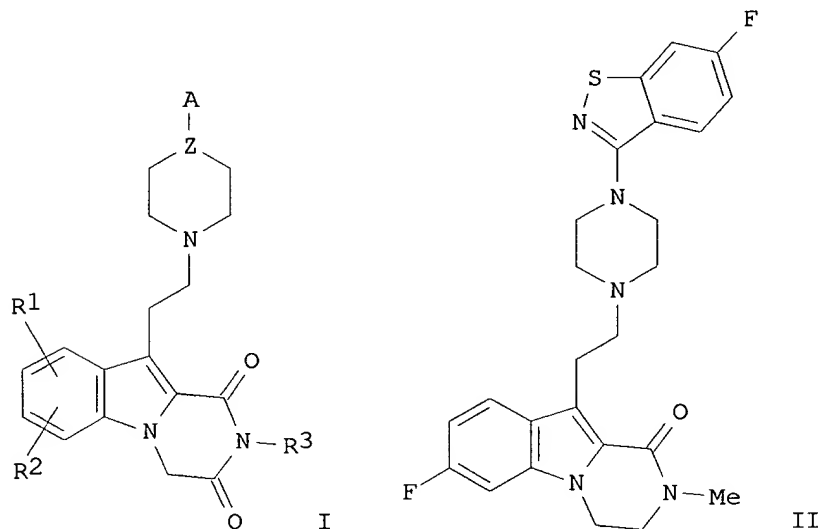
● 2 HCl

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 47 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:672550 HCAPLUS
DOCUMENT NUMBER: 129:275933
TITLE: Dihydropyrazino[1,2-a]indol-1-one derivatives,
preparation, and application thereof in therapeutics
as serotonin antagonists
INVENTOR(S): McCort, Gary; Hoornaert, Christian; Cadilhac,
Caroline; Duclos, Olivier; Guilpain, Eric; Dellac,
Genevieve
PATENT ASSIGNEE(S): Synthelabo, Fr.
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Searched by Thom Larson, STIC, 308-7309

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9842710 | A1 | 19981001 | WO 1998-FR529 | 19980317 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| FR 2761070 | A1 | 19980925 | FR 1997-3389 | 19970320 |
| FR 2761070 | B1 | 19990423 | | |
| AU 9869240 | A1 | 19981020 | AU 1998-69240 | 19980317 |
| EP 971926 | A1 | 20000119 | EP 1998-914929 | 19980317 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI | | | | |
| ZA 9802369 | A | 19980923 | ZA 1998-2369 | 19980319 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | FR 1997-3389 | 19970320 |
| | | | WO 1998-FR529 | 19980317 |
| OTHER SOURCE(S): MARPAT 129:275933 | | | | |
| GI | | | | |



AB The invention concerns title compds. I [in which R1, R2 = H, halo, NH2, OH, NO2, CN, (C1-6)alkyl, (C1-6)alkoxy, CF3, OCF3, COOH, COOR4, CONH2, CONHR4, CONR4R5, SR4, SO2R4, NHCOR4, NHSO2R4, N(R4)2 [R4, R5 = (C1-4)alkyl]; R3 = H, (C1-6)alkyl, (CH2)pOH, (CH2)nCH(OH)(CH2)nOH, (CH2)pNH2, (CH2)pNHR7 [R7 = C(:NH)NH2], (CH2)nCOOH, (CH2)nCOOR4, (CH2)nCN, (CH2)n-tetrazol-5-yl, (CH2)nCONH2, (CH2)nCONHR8 [R8 = OH, (C1-4)alkoxy, or 1-methylpiperidin-4-yl], (CH2)nCONH(CH2)nR9 [R9 = OH or NR4R5], (CH2)nCONAA (AA = amino acid), (CH2)pSH, (CH2)nSO3H, (CH2)nSO2NH2, (CH2)nSO2NHR4, (CH2)nSO2NR4R5, (CH2)nCONHR4, (CH2)nCONR4R5, (CH2)pNH2SO2R4, (CH2)pNHCOR4, (CH2)pOCOR4 [n = 1-4 and p = 2-4]; Q = 2H or O; Z = N or CH;

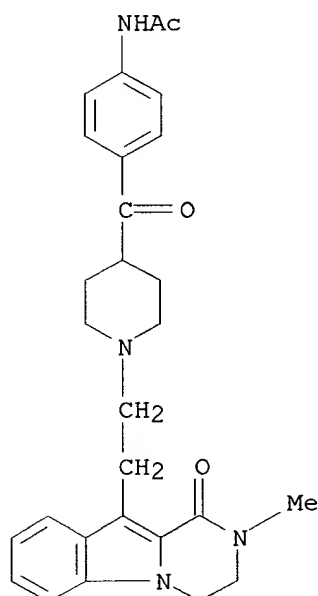
A = (un)substituted benzoyl, 1H-indazol-3-yl, 1,2-benzisoxazol-3-yl, or 1,2-benzisothiazol-3-yl]. The compds. have serotonin antagonist properties, and have a variety of cardiovascular uses, such as treatment of different forms of hypertension, ischemia, angina, vasospasm, atherosclerosis, etc. For instance, 10-(2-chloroethyl)-7-fluoro-2-methyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one was prepd. in 8 steps, and 6-fluoro-3-(piperazin-1-yl)-1,2-benzisothiazole was prepd. in 6 steps. These 2 compds. were coupled using NaHCO₃ in MeCN-DMF mixt. to give 36% title compd. II. The compds. inhibited binding of [3H]-spiroperidol to rat cerebral 5-HT₂ receptors in vitro with IC₅₀ < 1 .mu.M.

IT **213885-83-7P 213885-85-9P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of dihydropyrazinoindolone derivs. as serotonin antagonists)

RN 213885-83-7 HCAPLUS

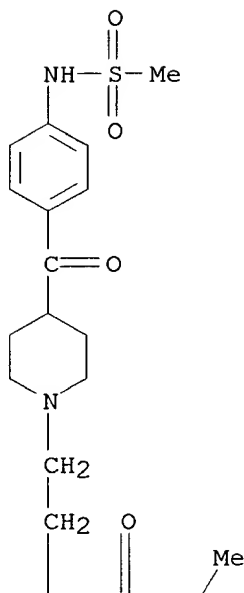
CN Acetamide, N-[4-[[1-[2-(1,2,3,4-tetrahydro-2-methyl-1-oxopyrazino[1,2-a]indol-10-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



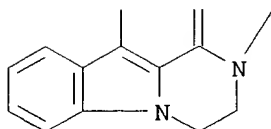
RN 213885-85-9 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(1,2,3,4-tetrahydro-2-methyl-1-oxopyrazino[1,2-a]indol-10-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI)
(CA INDEX NAME)

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L14 ANSWER 48 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:634940 HCAPLUS
DOCUMENT NUMBER: 129:327366
TITLE: Transfer of rapid inactivation and sensitivity to the
class III antiarrhythmic drug E-4031 from HERG to
M-eag channels
AUTHOR(S): Herzberg, Ian M.; Trudeau, Matthew C.; Robertson, Gail
A.
CORPORATE SOURCE: Department of Physiology, University of
Wisconsin-Madison Medical School, Madison, WI, 53706,
USA
SOURCE: Journal of Physiology (Cambridge, United Kingdom)
(1998), 511(1), 3-14
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1. The gating behavior and pharmacol. sensitivity of HERG are remarkably
different from the corresponding properties of M-eag, a structurally

Searched by Thom Larson, STIC, 308-7309

similar member of the Eag family of potassium channels. In contrast to HERG, M-eag exhibits no apparent inactivation and little rectification, and is insensitive to the class III antiarrhythmic drug E-4031. 2. We generated chimeric channels of HERG and M-eag sequences and made point mutations to identify the region necessary for rapid inactivation in HERG. This region includes the P region and half of the S6 putative transmembrane domain, including sites not previously assocd. with inactivation and rectification in HERG. 3. Transfer of a small segment of the HERG polypeptide to M-eag, consisting largely of the P region and part of the S6 transmembrane domain, is sufficient to confer rapid inactivation and E-4031 sensitivity to M-eag. This region differs from the corresponding region in M-eag by only fifteen residues. 4. Previous hypotheses that rapid inactivation of HERG channels occurs by a C-type inactivation mechanism are supported by the parallel effects on rates of HERG inactivation and Shaker C-type inactivation by a series of mutations at two equiv. sites in the polypeptide sequences. 5. In addn. to sites homologous to those previously described for C-type inactivation in Shaker, inactivation in HERG involves a residue in the upstream P region not previously assocd. with C-type inactivation. Although this site is equiv. to one implicated in P-type inactivation in Kv2.1 channels, our data are most consistent with a single, C-type inactivation mechanism.

IT 113559-13-0, E-4031

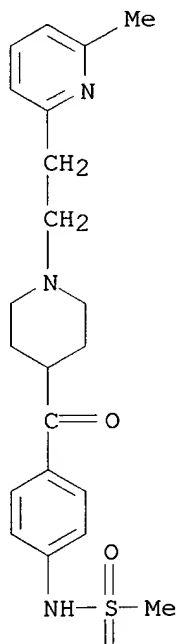
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(transfer of rapid inactivation and sensitivity to the class III antiarrhythmic drug E-4031 from HERG to M-eag channels)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

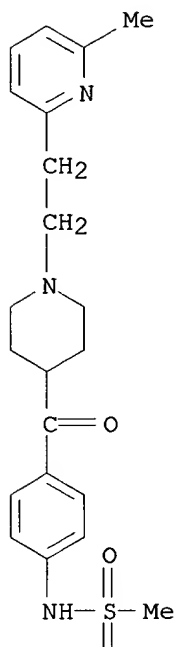
L14 ANSWER 49 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1998:606027 HCAPLUS
 DOCUMENT NUMBER: 130:10436
 TITLE: Comparison of effects of quinidine and E-4031 on
 aconitine and strophanthin G-induced cardiac
 arrhythmia in rats and guinea pigs
 AUTHOR(S): Zhang, Qiong; Wang, Xiao-Liang
 CORPORATE SOURCE: Institute of Materia Medica, Chinese Academy of
 Medical Sciences, Peking Union Medical College,
 Beijing, 100050, Peop. Rep. China
 SOURCE: Zhongguo Yaolixue Yu Dulixue Zazhi (1998), 12(3),
 181-183
 CODEN: ZYYZEW; ISSN: 1000-3002
 PUBLISHER: Zhongguo Yaolixue Yu Dulixue Zazhi Biarjibu
 DOCUMENT TYPE: Journal
 LANGUAGE: Chinese

AB The purpose of this study was to investigate the relationship between the
 K⁺ channel subtype selectivity and antiarrhythmic effects of quinidine and
 E-4031 [N-(4-[(1-[2-(6-methyl-2-pyridyl) ethyl]-4-piperidyl)-carbonyl]
 phenyl) methanesulfonamide dihydrochloride dihydrate]. In comparison with
 the effects of quinidine (antiarrhythmic agents with Ito blockade) and
 E-4031 (a potent I_k blocker) on aconitine-induced cardiac arrhythmia in
 rats and strophanthin G-induced arrhythmia in guinea pigs. The results
 showed that quinidine was effective to prevent against arrhythmia in rats
 at dose of 10 mg. kg⁻¹, but E-4031 was not effective at the dose of 30
 .mu.g.kg⁻¹. However, in guinea pigs, E-4031 was effective at the dose of
 3 .mu.g.kg⁻¹. Quinidine was not effective until at higher dose of 30
 mg.kg⁻¹. The results suggest that the different effects of these two
 drugs on the two animal models are related to their channel subtype
 selectivity and implies that the cardiac Ito may be a target of some
 antiarrhythmia agents.

IT **113559-13-0**, E-4031
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (comparison of effects of quinidine and E-4031 on aconitine and
 strophanthin G-induced cardiac arrhythmia in rats and guinea pigs)

RN 113559-13-0 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
 piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 50 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:574629 HCAPLUS
DOCUMENT NUMBER: 129:339658
TITLE: Comparative electrophysiologic findings between
responders and nonresponders to class III
antiarrhythmic drugs among patients with ventricular
tachyarrhythmia
AUTHOR(S): Naitoh, Naoki; Washizuka, Takashi; Takahashi,
Kazuyoshi; Miyajima, Takefumi; Aizawa, Yoshifusa
CORPORATE SOURCE: First Department of Internal Medicine, Niigata
University School of Medicine, Niigata, 951, Japan
SOURCE: Japanese Heart Journal (1998), 39(3), 307-319
CODEN: JHEJAR; ISSN: 0021-4868
PUBLISHER: Japanese Heart Journal Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Electrophysiol. testing was performed in 31 patients with ventricular

Searched by Thom Larson, STIC, 308-7309

tachycardia (21 cases) and fibrillation (10 cases) to characterize the electrophysiol. properties of patients responding or not responding to therapy with class III antiarrhythmic drugs. At the baseline, there were no differences among the patients in the monomorphic VT cycle length (CL), block CL or the width of the zone of entrainment. Ventricular tachyarrhythmias after the administration of class III drugs (sotalol: 9, amiodarone: 15 and E-4031/MS-551: 7) were inducible (non-responders) in 17 patients and non-inducible (responders) in 14 (45%). The class III drugs prolonged the sinus cycle length (SCL), QT interval and right ventricular effective refractory period (VERP), but had little effect on ventricular conduction time in the responders and non-responders. The SCL, QT interval and VERP at the three drive cycle lengths of 600, 400 and 300 ms were significantly longer in the responders than in the non-responders, but the class III drug action on VERP showed a reverse use-dependency. Isoproterenol administered to the responder did not fully reverse the class III antiarrhythmic drug-induced prolongation of QT, QTc and VERP, which remained significantly prolonged compared to the baseline values. Furthermore, when the VERP after the administration of class III drugs were greater than 270, 250 and 240 ms at the three drive cycle lengths of 600, 400 and 300 ms, resp., it was assocd. with the non-inducibility of VT/VF. Though the precise mechanism of the drug efficacy is not yet known, these observations help to clarify the ability of class III drugs to prevent the induction of ventricular tachyarrhythmia.

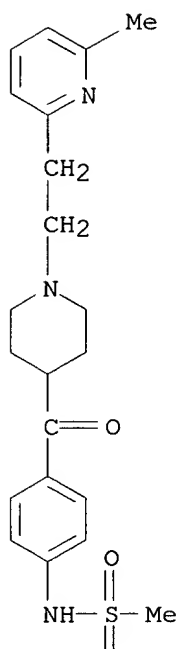
IT 113559-13-0, E-4031

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative electrophysiol. findings between responders and nonresponders to class III antiarrhythmic drugs among humans with ventricular tachyarrhythmia)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 51 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:508537 HCAPLUS
DOCUMENT NUMBER: 129:225501
TITLE: Antiarrhythmic effects of a novel class III drug, KCB-328, on canine ventricular arrhythmia models
AUTHOR(S): Xue, Yixue; Tanabe, Shigeru; Nabuchi, Yoshiaki; Hashimoto, Keitaro
CORPORATE SOURCE: Department of Pharmacology, Yamanashi Medical University, Yamanashi, 409-3898, Japan
SOURCE: Journal of Cardiovascular Pharmacology (1998), 32(2), 239-247
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB KCB-328 is a newly synthesized class III drug. To det. whether this drug has antiarrhythmic or proarrhythmic effects, the authors used canine ventricular arrhythmia models induced by coronary ligation and

Searched by Thom Larson, STIC, 308-7309

reperfusion, programmed elec. stimulation (PES), two-stage coronary ligation, digitalis, or epinephrine. KCB-328, in an i.v. infusion of 0.5 mg/kg/30 min, prolonged the QTc interval only 11%, but had antiarrhythmic effects on the reentry arrhythmias induced by PES (12 of 12 dogs with old myocardial infarction; $p < 0.05$). KCB-328, in an infusion of 1 mg/kg/h, suppressed the occurrence of fatal ventricular fibrillation (VF) induced by coronary ligation and reperfusion under either halothane anesthesia ($p < 0.05$) or pentobarbital anesthesia ($p < 0.05$). Under the halothane anesthesia, KCB-328 alone showed proarrhythmic effects [i.e., induction of ventricular premature contractions (VPCs)], but it did not induce a more severe effect such as torsades de pointes-type ventricular tachycardia (VT). In addn., KCB-328 had weak antiarrhythmic effects on the automaticity arrhythmias induced by 24-h coronary ligation but was effective neither on 48-h coronary ligation arrhythmias nor on the digitalis- and epinephrine-induced arrhythmias. The results indicate that KCB-328 has powerful antiarrhythmic effects with fewer proarrhythmic potencies.

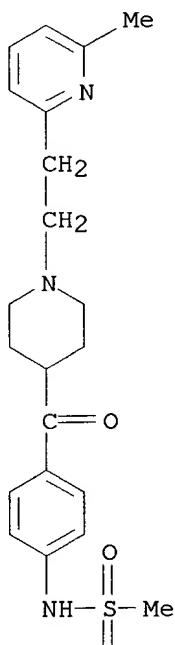
IT 113559-13-0, E-4031

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiarrhythmic effects of a novel class III drug, KCB-328, on canine ventricular arrhythmia models)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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L14 ANSWER 52 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:487735 HCAPLUS

DOCUMENT NUMBER: 129:170324

TITLE: Effect of E4031, a class III antiarrhythmic drug, on ischemia- and reperfusion-induced arrhythmias in isolated rat hearts

AUTHOR(S): Shinmura, Ken; Tani, Masato; Hasegawa, Hiroshi; Ebihara, Yoshinori; Nakamura, Yoshiro

CORPORATE SOURCE: Department of Geriatric Medicine, Keio University School of Medicine, Tokyo, 160, Japan

SOURCE: Japanese Heart Journal (1998), 39(2), 183-197
CODEN: JHEJAR; ISSN: 0021-4868

PUBLISHER: Japanese Heart Journal Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The delayed outward rectifier K⁺ channel has a role in the increase in automaticity of myocytes under pathophysiol. conditions. The purpose of the present study was to clarify the effect of blockade of outward rectifier K⁺ channels by a class III antiarrhythmic drug, E4031, on ischemia- and reperfusion-induced arrhythmias. Ion fluxes, energy metabolites and cardiac function were measured and the epicardial electrocardiograms of Langendorff-perfused rat hearts were recorded during initial perfusion, global or regional ischemia and reperfusion. 10⁻⁷ M of E4031 administered during the initial perfusion did not prolong the QT interval, but slowed the heart rate (Control: 222, E4031: 183 bpm), increased myocardial 45Ca²⁺ uptake (Control: 2.1, E4031: 2.9 .mu.mol/g dwt) and attenuated the loss of intracellular K⁺ during ischemia (Control: 238, E4031: 248 .mu.mol/g dwt). E4031 tended to reduce ischemia-induced ventricular tachyarrhythmias (Control: 60, E4031: 30%, n.s.), but reperfusion-induced ventricular tachyarrhythmias were sustained longer by the administration of E4031 (Control: 255, E4031: 623 s). Prior exposure to E4031 decreased the depletion of high energy phosphates during ischemia, but suppressed their recovery during reperfusion. These results suggest that the attenuated loss of K⁺ from the ischemic myocardium and the decrease in heart rate by E4031 contributed to the redn. of ischemia-induced arrhythmias. However, the increase in myocardial Ca²⁺ uptake and altered energy metab. may be responsible for the increase in reperfusion-induced arrhythmias.

IT 113559-13-0, E4031

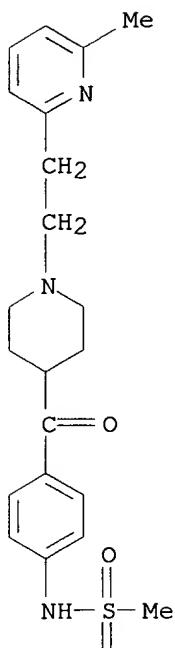
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of E4031 on ischemia- and reperfusion-induced arrhythmias in isolated rat hearts)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 53 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:441196 HCAPLUS
DOCUMENT NUMBER: 129:185648
TITLE: RERG is a molecular correlate of the inward-rectifying
K current in clonal rat pituitary cells
AUTHOR(S): Bauer, C. K.; Engeland, B.; Wulfsen, I.; Ludwig, J.;
Pongs, O.; Schwarz, J. R.
CORPORATE SOURCE: Physiologisches Institut, Universitäts-Krankenhaus
Eppendorf, Hamburg, D-20246, Germany
SOURCE: Receptors and Channels (1998), 6(1), 19-29
CODEN: RCHAE4; ISSN: 1060-6823
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The rat homolog of the human ether-a-go-go-related gene (r-erg) was cloned
from rat brain using homol. screening. RERG has a 96% amino acid identity
to HERG. Membrane currents recorded in CHO cells after previous injection

of r-erg showed that the voltage- and time-dependent properties are indistinguishable from h-erg-induced currents expressed in the same system. RT-PCR revealed the presence of r-erg mRNA in clonal rat pituitary cells (GH3/B6 cells). These cells exhibit a voltage-dependent inward-rectifying K current (IK.1R) which is highly sensitive to the class III antiarrhythmic E-4031. IK.1R recorded in GH3/B6 cells and ERG currents in CHO cells were compared using similar exptl. conditions (same pulse protocols and isotonic KCl as extracellular soln.). The voltage- and time-dependent properties of both currents were found to be almost identical. These results strongly suggest that RERG channels mediate IK.1R in GH3/B6 cells.

IT **113559-13-0**, e-4031

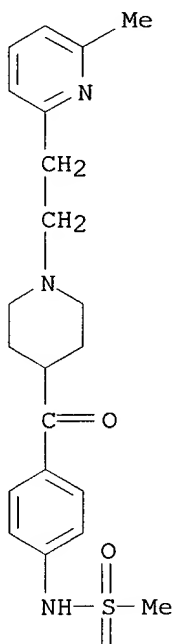
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(channel highly sensitive to class III antiarrhythmic E-4031; RERG is mol. correlate of inward-rectifying K current in clonal rat pituitary cells)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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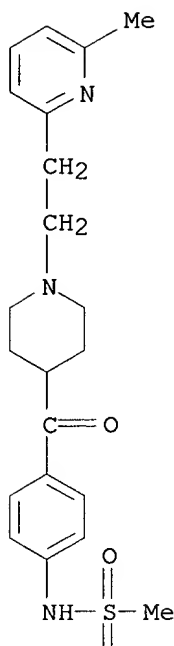
PAGE 2-A

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L14 ANSWER 54 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:403590 HCAPLUS
DOCUMENT NUMBER: 129:156693
TITLE: Development of pharmacophores for inhibitors of the
rapid component of the cardiac delayed rectifier
potassium current
AUTHOR(S): Matyus, Peter; Borosy, Andras P.; Varro, Andras; Papp,
Julius G.; Barlocco, Daniela; Cignarella, Giorgio
CORPORATE SOURCE: Institute of Organic Chemistry, Semmelweis University
of Medicine, Budapest, H-1092, Hung.
SOURCE: International Journal of Quantum Chemistry (1998),
69(1), 21-30
CODEN: IJQCB2; ISSN: 0020-7608
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Blockade of cardiac-delayed rectifier potassium current (IKr) is an
important mechanism for Class III antiarrhythmic effect. We developed
pharmacophores for IKr inhibitors starting from structures of known
blockers. To obtain the pharmacophores, DISCO module of SYBYL was used.
Conformations required for DISCO computations were provided by Multisearch
type conformational analyses. A common five-point three-dimensional
relationship was identified for the most active compds., whereas a
four-point pharmacophore forming a subset of the former one, could be
developed for less potent agents.
IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(pharmacophore development for inhibitors of rapid component of cardiac
delayed rectifier potassium current)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 55 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1998:394803 HCAPLUS
 DOCUMENT NUMBER: 129:117986
 TITLE: Effects of gonadal steroids on ventricular repolarization and on the response to E4031
 AUTHOR(S): Hara, Motoki; Danilo, Peter, Jr.; Rosen, Michael R.
 CORPORATE SOURCE: Departments of Pharmacology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 285(3), 1068-1072
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Gonadal steroids are thought to be important determinants of gender-related differences in electrophysiol., such as the longer rate-cor. QTc intervals in women and the incidences of some clin. arrhythmias. The authors studied the chronic effects of gonadal steroids

Searched by Thom Larson, STIC, 308-7309

on cardiac action potentials (APs) using std. electrophysiol. techniques. Papillary muscles were removed from the hearts of oophorectomized rabbits that had been treated with placebo, estradiol or dihydrotestosterone (DHT). The electrocardiograms of the three groups did not differ. Papillary muscle APs were studied during drive at cycle lengths of 330 to 5000 ms. The APD30 of the DHT group was significantly shorter than that of the others at cycle lengths of >500 ms. The APD90 of the estradiol group was significantly longer than that of the DHT group at cycle lengths of >1000 ms. The APD90 of the placebo group tended to be intermediate. The effects of the antiarrhythmic drug E4031 (10⁻⁸-10⁻⁶ M) also were examd. E4031-induced prolongation of APD90 and magnitude of early after depolarizations was significantly greater in the estradiol-treated than the DHT-treated and placebo groups. In conclusion, in rabbit heart, gonadal steroids are important determinants of base-line electrophysiol. properties and the proarrhythmic response to E4031.

IT 113559-13-0, E4031

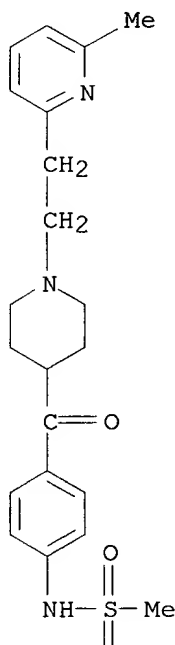
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of gonadal steroids on ventricular repolarization and on the response to E4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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L14 ANSWER 56 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:244887 HCAPLUS
DOCUMENT NUMBER: 129:12499
TITLE: Differential atrial versus ventricular activities of
class III potassium channel blockers
AUTHOR(S): Baskin, Elizabeth P.; Lynch, Joseph J., Jr.
CORPORATE SOURCE: Merck Research Laboratories, Department of
Pharmacology, West Point, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics
(1998), 285(1), 135-142
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

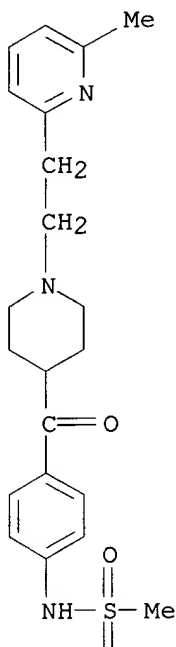
AB The atrial vs. ventricular activities of Class III agents with differing
K⁺ channel blocking profiles were assessed in vitro in ferret atrial and
right ventricular papillary muscles. In concn.-effective refractory
period (ERP) response studies at 2 Hz and 32.degree.C, the selective IKr
blockers dofetilide, E-4031 and d-sotalol, as well as ibutilide, an IKr
blocker also reported to enhance inward Na⁺ current, displayed markedly
greater efficacies in increasing atrial ERP (+90-110%) vs. ventricular ERP
(+10-20%). RP58866, a blocker of IK1 and IKr, and tedisamil, primarily a
blocker of Ito and IKr, increased atrial ERP with approx. 10-fold greater
potencies than ventricular ERP, but with similar efficacies for both
tissues (+60-80% with RP58866; +150-160% with tedisamil). Azimilide, a
blocker of IKr and IKs, and indapamide, a blocker of IKs, displayed
essentially "balanced" activities, increasing atrial and ventricular ERP
with equiv. potencies and efficacies (+40-60% increases for both tissues).
Frequency-dependence profiles at 32.degree.C varied between atrial and
ventricular tissues, and there was no general correspondence between
atrial vs. ventricular selectivity and frequency-dependence profiles. In
the papillary muscle prepn., increasing temp. from 32.degree.C to
37.degree.C altered both magnitude and frequency dependence of response to
K⁺ channel blockers. These findings support the potential to selectively
modulate atrial vs. ventricular refractoriness with the targeting of
appropriate K⁺ channel subtypes, and further demonstrate the differential
frequency and temp. dependence of varying K⁺ channel subtype blockade.
Ultimately, the identification and targeting of an appropriate K⁺ channel
subtype or mix of subtypes may result in the achievement of optimal
atrial-selective activity for the treatment of supraventricular
arrhythmias.

IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(class III potassium channel blockers atrial vs. ventricular activities
in isolated ferret myocardium)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



●2 HCl

L14 ANSWER 57 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:240869 HCAPLUS
DOCUMENT NUMBER: 129:349
TITLE: Comparative effects of glibenclamide, tedisamil, dofetilide, E-4031, and BRL-32872 on protein kinase A-activated chloride current in guinea pig ventricular myocytes
AUTHOR(S): Faivre, Jean-Francois; Rouanet, Sabine; Bril, Antoine
CORPORATE SOURCE: SmithKline Beecham Laboratoires Pharmaceutiques, Saint-Gregoire, Fr.
SOURCE: Journal of Cardiovascular Pharmacology (1998), 31(4), 551-557
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English

AB The modulation of the protein kinase A-activated chloride current (PKA-ICl) may lead to modification of the cardiac action potential shape. The purpose of this study was to evaluate the effects of glibenclamide, tedisamil, dofetilide, E-4031, and BRL-32872 on the PKA-ICl. Expts. were conducted by using the patch-clamp technique in guinea pig ventricular myocytes. PKA-ICl was activated by application of 1 .mu.M isoproterenol and was inhibited by 1 .mu.M propranolol, 10 .mu.M acetylcholine, or 1 mM 4-acetamido-4'-isothiocyanatostilbene-2,2'-disulfonic acid (SITS). The sulfonylurea receptor inhibitor, glibenclamide, inhibited PKA-ICl at micromolar concn. Among class III antiarrhythmic agents, tedisamil induced a dose-dependent inhibition of PKA-ICl with a half effective concn. (EC50) of 7.15 pM (Hill coeff., 0.54). This effect may contribute to action potential widening induced by tedisamil. In contrast, the selective inhibitors of the rapid component of the delayed rectifier K current (IKr), dofetilide, and E-4031, as well as BRL-32872, that blocks IKr, and the L-type calcium current, did not significantly affect the amplitude of PKA-ICl, even at high concns. (10-30 .mu.M). These results demonstrate that compds. such as glibenclamide and tedisamil that are known to block the ATP-sensitive K current also affect PKA-ICl. Furthermore it appears that blockade of PKA-ICl, is not a common feature for all class III antiarrhythmic agents.

IT 113559-13-0, E-4031

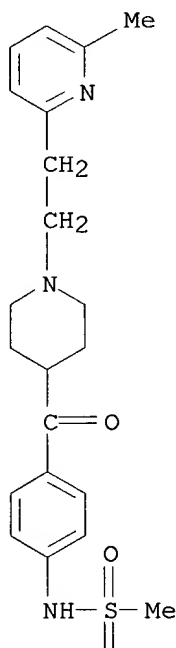
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(comparative effects of glibenclamide and class III antiarrhythmics tedisamil and dofetilide and E-4031 and BRL-32872 on protein kinase A-activated chloride current in guinea pig ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



Searched by Thom Larson, STIC, 308-7309

PAGE 2-A

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●2 HCl

L14 ANSWER 58 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:215868 HCAPLUS

DOCUMENT NUMBER: 128:252782

TITLE: Blockade of delayed K⁺ channel by two type III antiarrhythmics and its computer simulation

AUTHOR(S): Maruyama, Yasuyuki; Hangai, Kyoko; Nakamura, Yasuhiko; Midera, Takayuki; Yamakawa, Takeshi; Endoh, Goro; Koyama, Yutaka; Furukawa, Taiji; Yamanaka, Masami

CORPORATE SOURCE: Dep. Medicine, Teikyo Univ. Sch. Med., Tokyo, 173, Japan

SOURCE: Teikyo Igaku Zasshi (1997), 20(6), 487-500

CODEN: TIGZDZ; ISSN: 0387-5547

PUBLISHER: Teikyo Daigaku Igakubu

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB To elucidate the modes of action of type III anti-arrhythmic agents, the pharmacol. and electrophysiol. effects of two drugs E-4031 and MS-551 on rabbit sinoatrial and atrioventricular nodes were investigated. We re-analyzed the exptl. results, and raised a simple model for channel gating and drug-channel interaction by applying similar modeling to Na⁺ and Ca²⁺ channels. By a least squares fitting algorithm, the deactivation time course of the delayed rectifier potassium current (IK tail current) was represented as the sum of two exponential functions. This procedure revealed that both the drugs delayed the deactivating time course. According to our model, the drug bound IK channel worked as a reservoir of the open IK channel and the drugs delayed the IK tail current. The exptl. results were well reconstructed, when the time const. of drug-channel interaction for E-4031 was set at about a second, and that for MS-551 was set at about a few hundred msec. The results suggested that the binding and unbinding of MS-551 was faster than that of E-4031.

IT 113559-13-0, E-4031

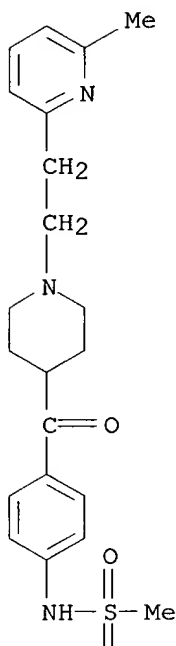
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(blockade of delayed K⁺ channel by two type III antiarrhythmics and its computer simulation)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 59 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:191086 HCAPLUS
DOCUMENT NUMBER: 128:319815
TITLE: Properties of HERG channels stably expressed in HEK 293 cells studied at physiological temperature
AUTHOR(S): Zhou, Zhengfeng; Gong, Qiuming; Ye, Bin; Fan, Zheng; Makielski, Jonathan C.; Robertson, Gail A.; January, Craig T.
CORPORATE SOURCE: Departments of Medicine (Cardiology) and Physiology, University of Wisconsin, Madison, WI, 53792, USA
SOURCE: Biophysical Journal (1998), 74(1), 230-241
CODEN: BIOJAU; ISSN: 0006-3495
PUBLISHER: Biophysical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have established stably transfected HEK 293 cell lines expressing high levels of functional human ether-a go-go-related gene (HERG) channels. We used these cells to study biochem. characteristics of HERG protein, and to

Searched by Thom Larson, STIC, 308-7309

study electrophysiol. and pharmacol. properties of HERG channel current at 35.degree.C. HERG-transfected cells expressed an mRNA band at 4.0 kb. Western blot anal. showed two protein bands (155 and 135 kDa) slightly larger than the predicted mol. mass (127 kDa). Treatment with N-glycosidase F converted both bands to smaller mol. mass, suggesting that both are glycosylated, but at different levels. HERG current activated at voltages pos. to -50 mV, max. current was reached with depolarizing steps to -10 mV, and the current amplitude declined at more pos. voltages, similar to HERG channel current expressed in other heterologous systems. C.d. at 35.degree.C, compared with 23.degree.C, was increased by more than twofold to a max. of 53.4 +/- 6.5 pA/pF. Activation, inactivation, recovery from inactivation, and deactivation kinetics were rapid at 35.degree.C, and more closely resemble values reported for the rapidly activating delayed rectifier K⁺ current (IKr) at physiol. temps. HERG channels were highly selective for K⁺. When we used an action potential clamp technique, HERG current activation began shortly after the upstroke of the action potential waveform. HERG current increased during repolarization to reach a max. amplitude during phases 2 and 3 of the cardiac action potential. HERG contributed current throughout the return of the membrane to the resting potential, and deactivation of HERG current could participate in phase 4 depolarization. HERG current was blocked by low concns. of E-4031 (IC₅₀ 7.7 nM), a value close to that reported for IKr in native cardiac myocytes. Our data support the postulate that HERG encodes a major constituent of IKr and suggest that at physiol. temps. HERG contributes current throughout most of the action potential and into the postrepolarization period.

IT 113559-13-0, E-4031

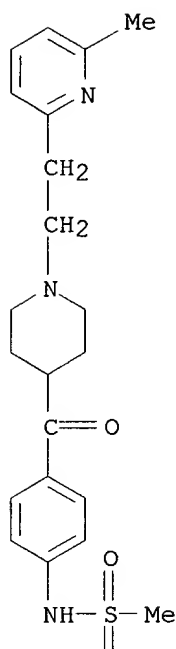
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(properties of HERG channels stably expressed in HEK 293 cells studied at physiol. temp. in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



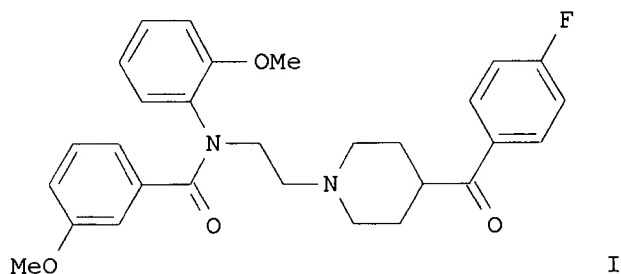
● 2 HCl

L14 ANSWER 60 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1998:186512 HCAPLUS
 DOCUMENT NUMBER: 128:230259
 TITLE: Preparation of N-(piperidinoalkyl)benzamides and
 analogs as 5-HT_{2A} antagonists
 INVENTOR(S): Aoki, Tsuyoshi; Takahashi, Atsuo; Sato, Hiroyasu;
 Shimanuki, Eiji; Gengyou, Kaoru; Nishimata, Toyoki;
 Ishigami, Sachiko; Yamada, Shin-ichi; Yamaguchi,
 Takahiro; Manome, Yoichi; Sato, Isamu; Kogi, Kentaro;
 Narita, Sen-ichi
 PATENT ASSIGNEE(S): Toa Eiyo, Ltd., Japan
 SOURCE: U.S., 59 pp., Cont.-in-part of U.S. Ser. No. 363,223,
 abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2

Searched by Thom Larson, STIC, 308-7309

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|-------------------|-----------------|----------|
| US 5728835 | A | 19980317 | US 1995-575062 | 19951219 |
| PRIORITY APPLN. INFO.: | | | JP 1993-346805 | 19931227 |
| | | | US 1994-363223 | 19941223 |
| OTHER SOURCE(S): | | MARPAT 128:230259 | | |
| GI | | | | |



AB R1Z1NR2(CH2)nZ2COR3 [I; R1 = (un)substituted Ph, -(N-oxido)pyridyl; R2 = (un)substituted Ph, -pyridyl; R3 = (un)substituted Ph; Z1 = CO or SO2; Z2 = piperidine-1,4-diyl; n = 2-3] were prep'd. Thus, 3-(MeO)C6H4COCl was amidated by 2-(MeO)C6H4NH2 and the product N-alkylated by 2-(2-bromoethyl)tetrahydropyran to give, after deprotection and oxidn., 3-(MeO)C6H4CON(CH2CHO)C6H4(OMe)-2 which was reductively condensed with 4-(4-fluorobenzoyl)piperidine to give title comp'd. II. Data for biol. activity of I were given.

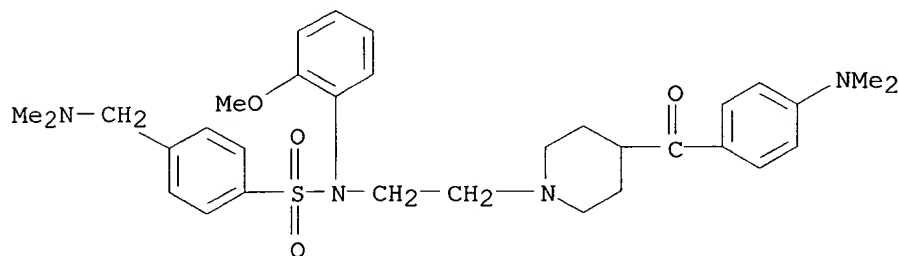
IT **169948-15-6P 169948-16-7P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-(piperidinoalkyl)benzamides and analogs as 5-HT2A antagonists)

RN 169948-15-6 HCAPLUS

CN Benzenesulfonamide, N-[2-[4-[4-(dimethylamino)benzoyl]-1-piperidinyl]ethyl]-4-[(dimethylamino)methyl]-N-(2-methoxyphenyl)- (9CI)
(CA INDEX NAME)



RN 169948-16-7 HCAPLUS

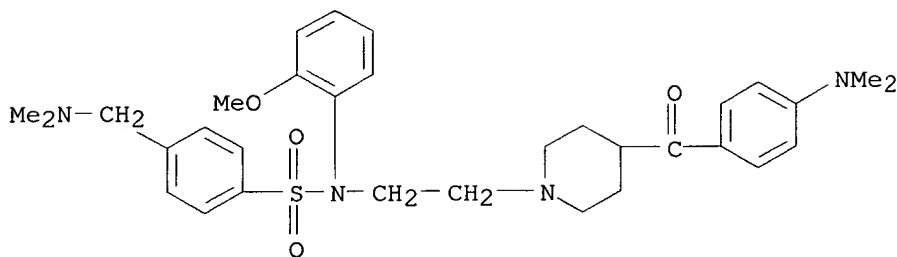
CN Benzenesulfonamide, N-[2-[4-[4-(dimethylamino)benzoyl]-1-piperidinyl]ethyl]-4-[(dimethylamino)methyl]-N-(2-methoxyphenyl)-,

ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 169948-15-6

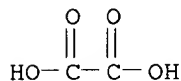
CMF C32 H42 N4 O4 S



CM 2

CRN 144-62-7

CMF C2 H2 O4



L14 ANSWER 61 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:65100 HCAPLUS

DOCUMENT NUMBER: 128:212924

TITLE: Inhibition of delayed rectifier K⁺ current by dofetilide and E-4031 differentially affects electrical cardiac responses to vagus stimulation in anesthetized dogs

AUTHOR(S): Imamura, Hiroshi; Furukawa, Yasuyuki; Kasama, Miho; Hoyano, Yuji; Yonezawa, Takanori; Chiba, Shigetoshi

CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, 390, Japan

SOURCE: Japanese Journal of Pharmacology (1998), 76(1), 31-37
CODEN: JJPAAZ; ISSN: 0021-5198

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vagal activation influences various cardiac functions as well as occurrence of arrhythmias. Inhibition of a rapid type of delayed rectifier K⁺ current (IKr) has been reported to be effective for the treatment of both ventricular and supraventricular arrhythmias. However, it is unknown how IKr inhibition modulates the cardiac responses to vagal activation in situ. The effects of 2 IKr inhibitors, dofetilide and E-4031, and a class I antiarrhythmic agent, disopyramide, on elec. cardiac responses to vagus stimulation were studied in anesthetized dogs. In unstimulated animals, dofetilide (0.003-0.3 .mu.mol/kg, i.v.), E-4031 (0.01-1 .mu.mol/kg, i.v.) and disopyramide (2.9-29 .mu.mol/kg, i.v.)

dose-dependently prolonged sinus cycle length (SCL), right-atrial effective refractory period (AERP) and ventricular effective refractory period (VERP). During cervical vagus stimulation-induced prolongation of SCL, atrio-His (AH) interval and VERP and shortening of AERP, dofetilide and E-4031 inhibited the prolongation of SCL but potentiated the shortening of AERP. Dofetilide and E-4031 did not affect the prolongations of AH interval and VERP. On the other hand, disopyramide inhibited all elec. cardiac responses to vagus stimulation. These results suggest that IKr inhibition differentially modulates cardiac responses to vagus activation, probably due to a different role of IKr in each cardiac function in the heart in situ.

IT 113559-13-0, E-4031

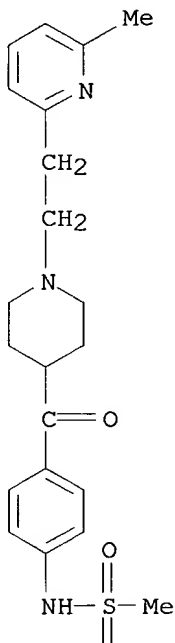
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(heart responses to vagal stimulation alteration by inhibition of delayed rectifier potassium current by)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



2 HCl

L14 ANSWER 62 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:30859 HCAPLUS

DOCUMENT NUMBER: 128:175989

TITLE: Inhibition by E-4031 of the prolongation of the first returning cycle length after overdrive in anesthetized dog hearts

AUTHOR(S): Nagashima, Yoshito; Furukawa, Yasuyuki; Hirose, Masamichi; Hoyano, Yuji; Lakhe, Manoj; Chiba, Shigetoshi

CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, 390, Japan

SOURCE: Journal of Cardiovascular Pharmacology (1998), 31(1), 18-24

CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Prolongation of the functional recovery of the sinoatrial (SA) nodal pacemaker activity after overdrive, "overdrive suppression," is detd. by intrinsic pacemaker activity, pacemaker site, and SA conduction. The authors investigated the effects of E-4031, a blocker of a rapid type of the delayed rectifier K⁺ current (I_{Kr}) and stimulation of the intracardiac parasympathetic nerves to the SA nodal region (SAP) on the prolongation of the first returning cycle length (1st RCL) after overdrive in autonomically decentralized hearts of open-chest anesthetized dogs. Second and third RCLs also were measured. The authors detd. SA node recovery time (SNRT) and cor. SNRT (CSNRT) after atrial pacing at rates of 120, 150, and 200% of the control rate for 1 min and also detd. SA conduction time (SACT) by the const.-atrial-pacing method. E-4031 (0.1-3 .mu.mol/kg i.v.) increased the sinus cycle length (SCL) and SNRT dose dependently. However, E-4031 decreased CSNRT when the pacing rate was low or the no. of pacing stimuli was small, although the agent did not induce a significant change in CSNRT when sufficient pacing stimuli were applied. E-4031 decreased SACT dose dependently. After E-4031 treatment, the authors obsd. changes in atrial elec. configurations, suggesting the possibility of pacemaker shift. When SAP stimulation increased SCL, SNRT, CSNRT, and SACT, E-4031 selectively inhibited the prolongation of SCL by SAP stimulation but did not affect the prolongation of CSNRT or SACT. These results suggest that functional recovery of the SA nodal pacemaker activity after overdrive is regulated by I_{Kr} at least in part and that I_{Kr} inhibition attenuates prolongation of the SCL but not the 1st RCL induced by parasympathetic nerve activation in the heart in situ.

IT 113559-13-0, E-4031

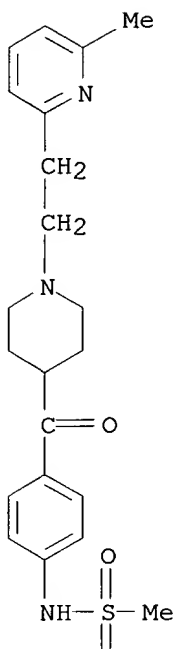
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(inhibition by E-4031 of prolongation of first returning cycle length after overdrive in anesthetized dog hearts)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 63 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:778168 HCAPLUS
DOCUMENT NUMBER: 128:84246
TITLE: Vesnarinone prolongs action potential duration without reverse frequency dependence in rabbit ventricular muscle by blocking the delayed rectifier K⁺ current
AUTHOR(S): Toyama, Junji; Kamiya, Kaichiro; Cheng, Jianhua; Lee, Jong-Kook; Suzuki, Ryoko; Kodama, Itsuo
CORPORATE SOURCE: Department of Circulation, Research Institute of Environmental Medicine, Nagoya (Japan) University, Nagoya, 464-01, Japan
SOURCE: Circulation (1997), 96(10), 3696-3703
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methanesulfonanilide derivs., selective inhibitors of the rapidly activating component (IKr) of the delayed rectifier potassium current

Searched by Thom Larson, STIC, 308-7309

(IK), prolong action potential duration (APD) of cardiac muscles with reverse frequency dependence, which limits their clin. use because of proarrhythmia. Vesnarinone, a quinolinone deriv. developed as a cardiotonic agent, has complex pharmacol. properties, but its clin. efficacy is explained in part by IK redn. Therefore, we investigated the mode of IK block by vesnarinone. IK of the rabbit ventricular myocyte was activated by voltage-clamp steps applied from a holding potential to various depolarizing levels. The development of IK block at depolarization (+10 mV) and its recovery process at hyperpolarization (-75 mV) were compared between vesnarinone and E-4031. The IK block by vesnarinone (3 $\mu\text{mol/L}$) developed and recovered monoexponentially, with time consts. of 361 ms (n=5) and 1.87 s (n=4), resp., IK block by E-4031 (0.3 $\mu\text{mol/L}$) developed instantaneously, with no recovery from the block at hyperpolarization. The IK block by vesnarinone, estd. by IK tail after a train of depolarizing pulses (for 30 s at 0.2 to 2 Hz), was increased with increasing frequency (twofold at 2 from 0.2 Hz), but that by E-4031 was unchanged. In rabbit papillary muscles, vesnarinone (10 $\mu\text{mol/L}$) prolonged APD at stimulation frequencies >0.2 Hz, whereas E-4031 (0.3 $\mu\text{mol/L}$) prolonged that in a reverse frequency-dependent manner. Vesnarinone may prolong the repolarization of human cardiac muscle without reverse frequency dependence, because IKr is expressed in humans as well as in the rabbit. Thus, this drug may be a model for an ideal class III drug without the risk of proarrhythmia.

IT 113559-13-0, E-4031

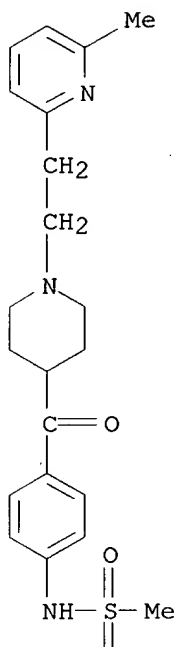
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(comparison with; vesnarinone prolongs action potential duration without reverse frequency dependence in rabbit ventricular muscle by blocking delayed rectifier K⁺ current)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 64 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1997:721444 HCAPLUS
 DOCUMENT NUMBER: 128:18527
 TITLE: Blocking effects of 6 antiarrhythmic drugs on
 transient outward current in rat ventricular myocytes
 AUTHOR(S): Liu, Qianrong; Wang, Xiaoliang
 CORPORATE SOURCE: Dep. of Pharmacol., Peking Union Med. Coll., Beijing,
 100050, Peop. Rep. China
 SOURCE: Yaoxue Xuebao (1997), 32(3), 183-187
 CODEN: YHHPAL; ISSN: 0513-4870
 PUBLISHER: Chinese Academy of Medical Sciences, Institute of
 Materia Media
 DOCUMENT TYPE: Journal
 LANGUAGE: Chinese
 AB The effects of 6 antiarrhythmic drugs on transient outward current (Ito)
 in rat ventricular myocytes were examd. using the patch-clamp whole-cell
 recording technique. Quinidine, nifedipine and imipramine showed
 concn.-dependent inhibition of Ito with IC50 of 5.4, 10.9 and 6.0 .mu.mol

L-1, resp. All 3 agents produced a concn.-dependent increase in the rate of inactivation of Ito. Disopyramide, procainamide and E-4031 produced little inhibition of Ito even at 100 .mu.mol L-1. The results suggest that quinidine, nifedipine and imipramine are potent inhibitors of Ito and that inhibition is mediated through preferential interaction with the open channel.

IT **113559-13-0**, E-4031

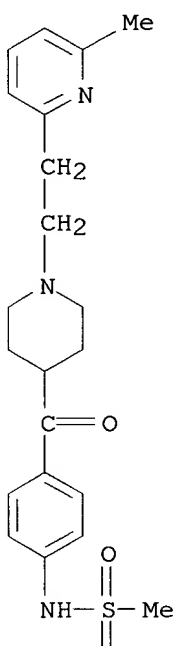
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(blocking effects of 6 antiarrhythmic drugs on transient outward current in rat ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 65 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:707297 HCAPLUS

Searched by Thom Larson, STIC, 308-7309

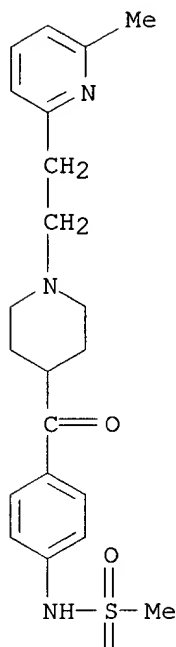
DOCUMENT NUMBER: 128:43598
TITLE: Modulation of HERG affinity for E-4031 by [K+]o and C-type inactivation
AUTHOR(S): Wang, Shimin; Morales, Michael J.; Liu, Shuguang; Strauss, Harold C.; Rasmusson, Randall L.
CORPORATE SOURCE: Departments of Medicine, Biomedical Engineering and Pharmacology, Duke University Medical Center, Durham, NC, USA
SOURCE: FEBS Letters (1997), 417(1), 43-47
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rectification of HERG is due to a rapid inactivation process that has been labeled C-type inactivation and is believed to be due to closure of the external mouth of the pore. We examd. the effects of mutation of extracellular residues that remove C-type inactivation on binding of the intracellularly acting methanesulfonanilide drug E-4031. Removal of inactivation through mutation reduced drug affinity by more than an order of magnitude. Elevation of [K+]o in the wild-type channel reduces channel affinity for E-4031. Elevation of [K+]o also interferes with the extracellular pore mouth closure assocd. with C-type inactivation through a 'foot in the door' mechanism. We examd. the possibility that [K+]o elevation reduces drug binding through inhibition of C-type inactivation by comparing drug block in the wild-type and inactivation-removed mutant channels. Elevation of [K+]o decreased affinity in both channel constructs by a roughly equal amt. These results suggest that [K+]o alters drug binding affinity independently of its effects on C-type inactivation. They further suggest that inhibition of pore mouth closure by elevated [K+]o does not have same effect on drug affinity as mutations removing C-type inactivation.

IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(potassium and C-type activation affect on human ether-a-go-go-related gene affinity for antiarrhythmic E-4031)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 66 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:689547 HCAPLUS
DOCUMENT NUMBER: 127:355340
TITLE: Combination of a potassium channel activator and an
antiarrhythmic agent for the concomitant treatment of
ischemia and arrhythmia
INVENTOR(S): D'Alonzo, Albert J.; Grover, Gary J.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S., 17 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| US 5679706 | A | 19971021 | US 1994-316153 | 19940930 |

Searched by Thom Larson, STIC, 308-7309

OTHER SOURCE(S): MARPAT 127:355340

AB A method for the concomitant treatment of ischemia and arrhythmia in mammalian species is disclosed which includes administering a combination of a potassium channel opener having little or no effect on action potential duration in the heart and a class III antiarrhythmic compd.

IT 113559-13-0, E 4031

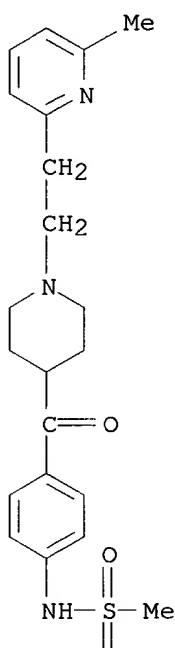
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(potassium channel opener-antiarrhythmic agent combination for concomitant treatment of ischemia and arrhythmia)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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PAGE 2-A



● 2 HCl

L14 ANSWER 67 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1997:561623 HCAPLUS
 DOCUMENT NUMBER: 127:229421

Searched by Thom Larson, STIC, 308-7309

TITLE: Modulation of the electrophysiologic actions of E-4031 and dofetilide by hyperkalemia and acidosis in rabbit ventricular myocytes

AUTHOR(S): West, Paul D.; Martin, Donald K.; Bursill, Jane A.; Wyse, Kenneth R.; Campbell, Terence J.

CORPORATE SOURCE: Departments of Cardiology and Clinical Pharmacology, St. Vincent's Hospital, Sydney, NSW 2010, Australia

SOURCE: Journal of Cardiovascular Pharmacology and Therapeutics (1997), 2(3), 205-212
CODEN: JCPTFE; ISSN: 1074-2484

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB E-4031 and dofetilide are new class III antiarrhythmic agents that inhibit the rapid component of the delayed rectifier potassium channel (IKr); however, the effectiveness of many antiarrhythmic drugs in ischemic conditions is uncertain. The authors modeled two components of ischemia, hyperkalemia (9.6 mM) and acidosis (pH 6.8), in voltage-clamped single rabbit ventricular myocytes to help det. the effect of ischemia on the action of these two drugs. In physiol. soln. both E-4031 and dofetilide blocked IKr and significantly reduced total outward current. In hyperkalemic soln., both E-4031 and dofetilide showed significantly reduced blockade of IKr, while in acidotic soln., dofetilide showed significantly reduced blockade of IKr and E-4031 showed a trend to reduced blockade. Neither drug significantly reduced total outward current in hyperkalemic or acidotic solns. In these conditions, E-4031 and dofetilide demonstrate reduced blockade of IKr, resulting in loss of class III effect. Furthermore, the complete loss of blocking effect on total outward current during simulated ischemia suggests increases of other repolarizing currents also contribute to loss of class III effect.

IT 113559-13-0, E-4031

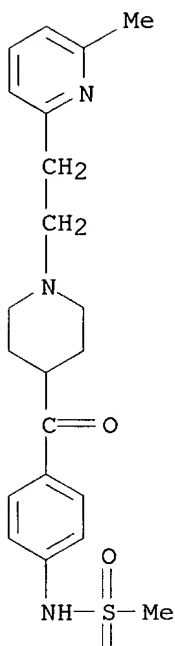
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(modulation of electrophysiol. actions of class III antiarrhythmics E-4031 and dofetilide by hyperkalemia and acidosis in rabbit ventricular myocytes in relation to ischemia and potassium channel blockade)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 68 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1997:506831 HCAPLUS
 DOCUMENT NUMBER: 127:149080
 TITLE: Piperidine derivatives as subtype-selective NMDA
 receptor ligands
 INVENTOR(S): Bigge, Christopher F.; Cai, Sui Xiong; Keana, John F.
 W.; Lan, Nancy C.; Guzikowski, Anthony P.; Zhou,
 Zhang-lin; Araldi, Gian Luca; Lamunyon, Donald; Weber,
 Eckard; et al.
 PATENT ASSIGNEE(S): Warner-Lambert Company, USA; Cocensys, Inc.
 SOURCE: PCT Int. Appl., 227 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
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Searched by Thom Larson, STIC, 308-7309

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|------------|----|----------|-----------------|----------|
| WO 9723458 | A1 | 19970703 | WO 1996-US20746 | 19961220 |
|------------|----|----------|-----------------|----------|

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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| ZA 9610738 | A | 19970624 | ZA 1996-10738 | 19961219 |
| AU 9713539 | A1 | 19970717 | AU 1997-13539 | 19961220 |
| US 6218404 | B1 | 20010417 | US 1998-91592 | 19980916 |
| US 2001051633 | A1 | 20011213 | US 2001-779024 | 20010207 |

PRIORITY APPLN. INFO.: US 1995-9185P P 19951222
WO 1996-US20746 W 19961220
US 1998-91592 A3 19980916

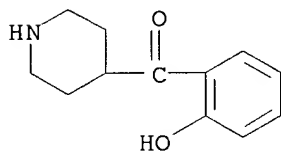
OTHER SOURCE(S): MARPAT 127:149080

AB Piperidine derivs. were prepd. as subtype-selective NMDA receptor ligands for use in characterizing these receptors and as neuroprotective agents. Thus, 4-benzylpiperidine was treated with Br(CH₂)₄CO₂Me, followed by NH₄OH to give 5-(4-benzylpiperidino)pentanamide (I). I had an 1A/2B IC₅₀ of 1.6 .mu.M.

IT **193204-77-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of piperidine derivs. as subtype-selective NMDA receptor ligands)

RN 193204-77-2 HCAPLUS

CN Methanone, (2-hydroxyphenyl)-4-piperidinyl-, hydrobromide (9CI) (CA INDEX NAME)

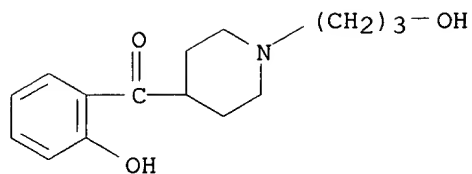


● HBr

IT **193204-78-3P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidine derivs. as subtype-selective NMDA receptor ligands)

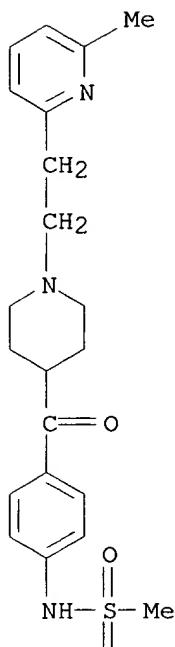
RN 193204-78-3 HCAPLUS

CN Methanone, (2-hydroxyphenyl)[1-(3-hydroxypropyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 69 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1997:457816 HCAPLUS
 DOCUMENT NUMBER: 127:75790
 TITLE: Frequency-dependent effect of vesnarinone, Ms-551 and E-4031 on the delayed rectifier potassium current in isolated rabbit ventricular myocytes
 AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Toyama, Junji
 CORPORATE SOURCE: Research Institute of Environmental Medicine, Nagoya University, Nagoya, 464-01, Japan
 SOURCE: Kankyo Igaku Kenkyusho Nenpo (Nagoya Daigaku) (1997), 48, 113-115
 CODEN: NDKIA2; ISSN: 0369-3570
 PUBLISHER: Nagoya Daigaku Kankyo Igaku Kenkyusho
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 AB The frequency-dependent effects of vesnarinone were compared with that of the type III antiarrhythmic Ms-551 and E-4031 on the delayed rectifier potassium current in isolated rabbit ventricular myocytes. The results are discussed with their effects on potassium channel.
 IT **113559-13-0**, E-4031
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (frequency-dependent effect of vesnarinone, Ms-551 and E-4031 on the delayed rectifier potassium current in isolated rabbit ventricular myocytes)
 RN 113559-13-0 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 70 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:384849 HCAPLUS
DOCUMENT NUMBER: 127:126701
TITLE: Development of simultaneous measurements of x-ray diffraction and DTA systems and application to the pharmaceutical solids
AUTHOR(S): Ashizawa, Kazuhide; Ishida, Mari; Utikawa, Kiyohiko; Ando, Hidenobu; Asakawa, Naoki
CORPORATE SOURCE: Preclinical Res. Lab., Pharmaceutical and Analytical Res. Div., Eisai Co., Ltd., Japan
SOURCE: Pharm Tech Japan (1997), 13(6), 881-887
CODEN: PTJAE9; ISSN: 0910-4739
PUBLISHER: Yakugyo Jihosha
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Development of simultaneous measurements of x-ray diffraction and DTA systems and application to the pharmaceutical solids e.g. crystallizable E4031 using .alpha.-cyclodextrin as vehicle are described. Unlike x-ray

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diffraction and DTA system alone, crystn. characteristics of E4031 and .alpha.-cyclodextrin can be easily detd. by x-ray diffraction and DTA combination. Results were satisfactory.

IT **113559-13-0**, E4031

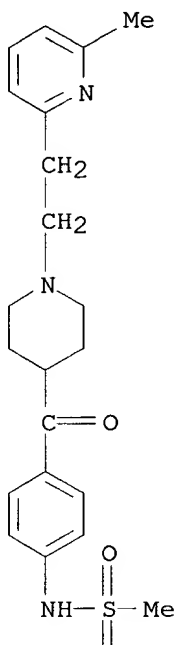
RL: ANT (Analyte); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(Development of simultaneous measurements of x-ray diffraction and DTA systems and application to the pharmaceutical solids)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 71 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:294293 HCAPLUS

DOCUMENT NUMBER: 127:60437

TITLE: The class III antiarrhythmic agent E-4031 selectively blocks the inactivating inward-rectifying potassium current in rat anterior pituitary tumor cells (GH3/B6)

Searched by Thom Larson, STIC, 308-7309

cells

AUTHOR(S): Weinsberg, Frank; Bauer, Christiane K.; Schwarz, Jurgen R.

CORPORATE SOURCE: Physiol. Inst., Krankenhaus Eppendorf, Hamburg, D-20246, Germany

SOURCE: Pfluegers Archiv (1997), 434(1), 1-10
CODEN: PFLABK; ISSN: 0031-6768

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

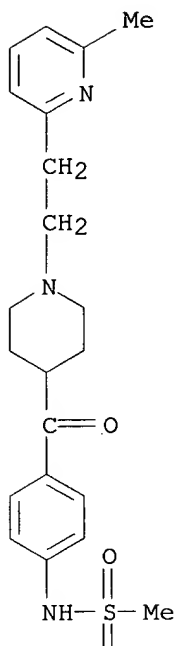
AB Hyperpolarization-elicited K currents in GH3/B6 cells bathed in high-K external soln. were recorded to assess effects of the class III anti-arrhythmic agent E-4031 on the inactivating inward-rectifying K current (IK,IR). E-4031 potently blocked IK,IR with an IC50 value of 10 nM. The complete block of IK,IR achieved with concns. .gtoreq. 1 .mu.M revealed the presence of a non-inactivating outward-rectifying current which contributed to the membrane currents recorded under control conditions. The time dependence of the IK,IR block depended on the concn. of E-4031. WAY-123,398 (10 .mu.M) also totally blocked IK,IR, while sotalol (100 .mu.M) was almost ineffective. Lanthanum (100 .mu.M) had only a very small effect on IK,IR. E-4031 did not affect Na, Ca, and voltage-de-pendent outward-rectifying K currents, suggesting a selective block of IK,IR in GH3/B6 cells. In an external soln. contg. 16 mM K, the E-4031-sensitive current was present as a steady outward current within a broad potential range pos. to the K equil. potential, EK. In many, but not all, cells E-4031 induced an increase in the frequency of action potentials suggesting an important role of IK,IR in controlling cell excitability. Thus, E-4031 is a valuable tool in characterizing IK,IR and its physiol. function.

IT **113559-13-0**, E 4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(E-4031 blocked inactivating inward-rectifying K current in rat anterior pituitary tumor cells (GH3/B6) cells)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 72 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:270775 HCAPLUS
DOCUMENT NUMBER: 126:325246
TITLE: Effects of class III antiarrhythmic drugs on transient outward and ultra-rapid delayed rectifier currents in human atrial myocytes
AUTHOR(S): Feng, Jianlin; Wang, Zhiguo; Li, Gui-Rong; Nattel, Stanley
CORPORATE SOURCE: Montreal Heart Institute, Univ. Montreal, Montreal, QC, Can.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 281(1), 384-392
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A variety of class III antiarrhythmic agents have been shown to block the delayed rectifier current, but their effects on other K⁺ currents,

Searched by Thom Larson, STIC, 308-7309

particularly in human tissues, are less clear. We studied the concn.-dependent actions of the class III compds. D-sotalol, E-4031 and ambasilide on the transient outward current (Ito) and the ultra-rapid delayed rectifier current (IKur) in human atrial myocytes. D-Sotalol and E-4031 failed to alter Ito or IKur at concns. up to 500 and 50 .mu.M, resp. In contrast, ambasilide produced a concn.-dependent inhibition of Ito and IKur, with statistically significant effects at 10 .mu.M and max. effects at 100 .mu.M. The 50% inhibitory concn. of ambasilide averaged 23 .+- . 2 .mu.M and 34 .+- . 2 .mu.M for Ito and IKur resp. Ambasilide did not alter the voltage-dependence of activation or inactivation of Ito, or the voltage-dependence of IKur, and it did not affect Ito recovery from inactivation. On the other hand, ambasilide accelerated Ito inactivation, by introducing a more rapid component that accelerated with increasing drug concn. Furthermore, block of both Ito and IKur developed over time after the onset of depolarization, with time consts. of 5.8 .+- . 0.8 ms and 2.5 .+- . 0.4 ms at concns. of 10 and 50 .mu.M for Ito and 6.1 .+- . 0.8 ms and 2.1 .+- . 0.3 ms at 10 and 50 .mu.M for IKur. We conclude that neither D-sotalol nor E-4031 affects Ito or IKur, whereas ambasilide produces efficacious open-channel block of both currents, in human atrial myocytes.

IT 113559-13-0, E-4031

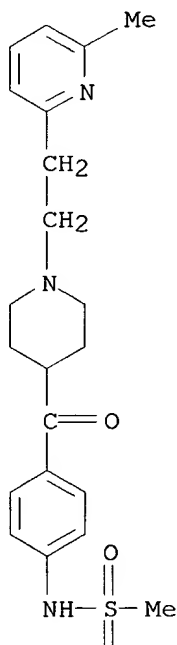
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of class III antiarrhythmics on transient outward and ultra-rapid delayed rectifier currents in human atrial myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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●2 HCl

L14 ANSWER 73 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:222211 HCAPLUS
DOCUMENT NUMBER: 126:301406
TITLE: Alkoxyfurocoumarin derivatives as potential mesolimbic
selective antipsychotics
AUTHOR(S): Hansen, J. Bondo; Fink-Jensen, A.; Hansen, L.;
Nielsen, E. B.; Scheideler, M. A.
CORPORATE SOURCE: Health Care Discovery, Novo Nordisk A/S, Malov,
DK-2760, Den.
SOURCE: European Journal of Medicinal Chemistry (1997), 32(2),
103-111
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

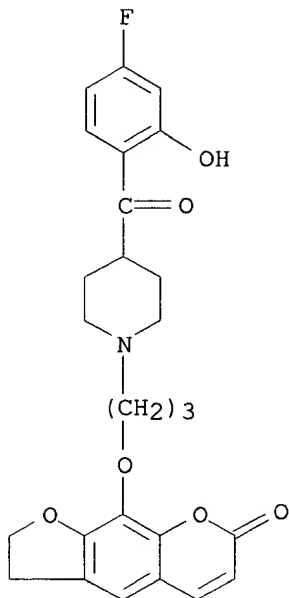
AB A series of potential antipsychotic compds. have been synthesized by
combining a furocoumarin heterocycle through a linker of different sizes
with an arylpiperazine or piperidine moiety. Several of the compds. show
very high affinity for the dopamine-D1 and -D2, .alpha.1-adrenergic and
serotonin 5-HT2 receptors in vitro and selected compds. were active in in
vivo models predictive of antipsychotic activity. In mice the compds.
potently antagonized methylphenidate-induced motility while
methylphenidate-induced gnawing was unaffected. In rats the compds.
inhibited condition avoidance responding without causing catalepsy.

IT **189261-50-5P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BSU (Biological study, unclassified); SPN (Synthetic
preparation); THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)
(prepn. of alkoxyfurocoumarin derivs. as potential mesolimbic selective
antipsychotics)

RN 189261-50-5 HCAPLUS
CN 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[3-[4-(4-fluoro-2-hydroxybenzoyl)-1-
piperidinyl]propoxy]-2,3-dihydro-, ethanedioate (1:1) (salt) (9CI) (CA
INDEX NAME)

CM 1

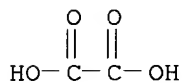
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CM 2

CRN 144-62-7

CMF C2 H2 O4



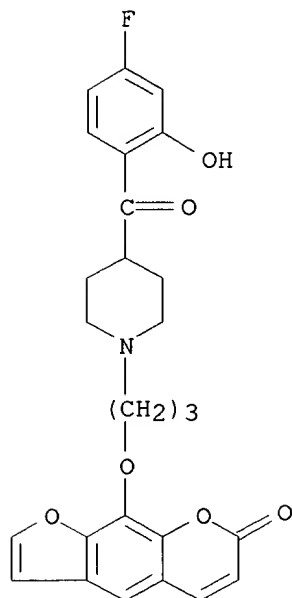
IT 189261-51-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; prepn. of alkoxyfurocoumarin derivs. as potential mesolimbic selective antipsychotics)

RN 189261-51-6 HCAPLUS

CN 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[3-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]propoxy]- (9CI) (CA INDEX NAME)



L14 ANSWER 74 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:209997 HCAPLUS

DOCUMENT NUMBER: 126:246618

TITLE: The novel class III antiarrhythmic agent MS-551 blocks the cardiac inward rectifier with greater potency than sotalol or E-4031: possible relevance to reverse use dependence

AUTHOR(S): Nakaya, Yutaka; Martin, Donald K.; Campbell, Terence J.

CORPORATE SOURCE: Departments of Cardiology and Clinical Pharmacology, St. Vincent's Hospital, Sydney, Australia

SOURCE: Journal of Cardiovascular Pharmacology and Therapeutics (1997), 2(1), 39-46
CODEN: JCPTFE; ISSN: 1074-2484

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The tendency for the electrophysiol. effect of class III antiarrhythmic agents (action potential prolongation) to be diminished at faster heart rates represents a major drawback of this class of drug and is usually referred to as "reverse use dependence.". A novel class III agent, MS-551, has recently been reported to exhibit less reverse use dependence than E-4031. The authors set out to investigate whether this observation may be due to differential blockade of the inward rectifier current (iK1) by these drugs. The authors recorded iK1 using single channel methods and cell attached patch configurations, with std. patch clamp technol. Neither E-4031 nor racemic sotalol in concns. .ltoreq.100 .mu.M had any significant effect on the open probability or kinetics of iK1 channels. MS-551 produced a concn.-dependent redn. in the open probability of iK1 without altering the single-channel conductance. Openings to subconductance levels were abolished in three of six patches in which they had been frequently present in the absence of drug. MS-551 had no effect on mean channel open time but increased the slower component of the closed

time. MS-551, unlike E-4031 and sotalol, appears to produce significant blockade of the inwardly rectifying potassium channel at clin. relevant concns. The authors propose that this might provide a partial explanation for the obsd. differences in their response to rate changes.

IT **113559-13-0**, E-4031

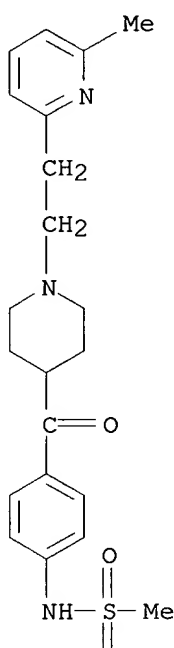
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(novel class III antiarrhythmic agent MS-551 blocks cardiac inward rectifier current with greater potency than sotalol or E-4031 and possible relevance to reverse use dependence in relation to potassium channel blockade)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 75 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:165902 HCAPLUS

Searched by Thom Larson, STIC, 308-7309

DOCUMENT NUMBER: 126:258394
TITLE: Effect of potassium channel blockers on isolated rat atrium
AUTHOR(S): Wang, Xiao-Liang; Hua, Zheng; Zhang, Ying
CORPORATE SOURCE: Inst. of Materia Medica, Chinese Acad. of Med. Sci. and Peking Union Med. Univ., Beijing, Peop. Rep. China
SOURCE: Drug Development Research (1996), 39(2), 161-166
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study describes a sensitive in vitro assay using isolated right atrium of adult Wistar rats to discover new compds. as K⁺ channel antagonists. For the purpose, several well-known K⁺ channel antagonists were investigated and compared with other compds. that modulate cardiac function. Potassium channel antagonists used in this study were barium chloride (BaCl₂), 4-aminopyridine (4-AP), tetraethylammonium (TEA), and E-4031. The concn.-dependent chronotropic and inotropic effect of K⁺ channel antagonists were detd. under physiol. condition and under depressed cardiac condition induced by stimulation of cholinergic M receptor with carbachol. Under physiol. conditions, these K⁺ channel antagonists showed a neg. chronotropic and pos. inotropic response. When the spontaneous beat rate was decreased by cholinergic stimulation, these agents enhanced the beat rate and the force of contraction simultaneously. Study on new compds. found that agents S94052 and S94056 were similar to the above K⁺ channel antagonists in functional response. Current and voltage-clamp study demonstrated that both new compds. prolonged the duration of action potential and reduced the steady-state K⁺ outward currents. The functional study described here can provide a sensitive and reproducible atrium model to discover new K⁺ channel antagonists.

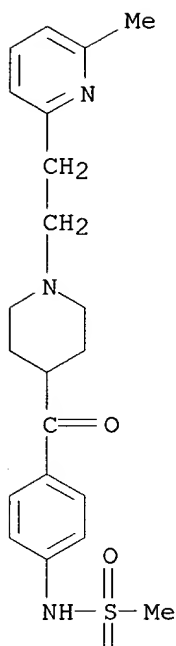
IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(isolated rat atrium in screening of potassium channel blockers)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 76 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:88986 HCAPLUS
DOCUMENT NUMBER: 126:155629
TITLE: Differential effects of chronic membrane depolarization on the K⁺ channel activities in cultured rat ventricular cells
AUTHOR(S): Guo, Weinong; Kamiya, Kaichiro; Toyama, Junji
CORPORATE SOURCE: Dep. Circulation, Nagoya Univ., Nagoya, 464-01, Japan
SOURCE: Cardiovascular Research (1997), 33(1), 139-146
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although there is widespread interest in the regulation of K⁺ channel gene expression by membrane depolarization, its effects on cardiac ion channel activity remain unclear. In the present study, the influences of chronic membrane depolarization on the functional expression of K⁺ channels in cultured rat cardiomyocytes were investigated. Single ventricular cells

isolated from day-old rat hearts were cultured for nearly 10 days. From day 6, chronic depolarization induced by elevating the K⁺ concn. of growth medium to 20 mM was developed for 72 h. Whole-cell patch-clamp techniques were used to record action potentials and ion currents. Compared with controls, longer action potential durations assocd. with relatively pos. resting potentials were obsd. after 72-h high K⁺ incubation. Chronic membrane depolarization caused a significantly reduced d. of transient outward current (I_{to}) without affecting the channel kinetics and voltage-dependence. Delayed rectifier K⁺ current (I_K) in cultured cells could be inhibited by E-4031, showing the drug-sensitive and -resistant components with different kinetic properties. The E-4031-sensitive current activated rapidly, and the drug-resistant current was characterized by slow activation. Both the rapid (I_{Kr}) and slow (I_{Ks}) components constituted I_K recorded from the control and depolarization-treated cells, while in the latter group the c.d. of I_{Kr} was slightly increased and that of I_{Ks} was enhanced by 80% with a small hyperpolarizing shift (5 mV) in the voltage-dependent activation curve. These observations suggest that the effects of chronic membrane depolarization differ depending on the phenotype of the cardiac K⁺ channels.

IT **113559-13-0**, E-4031

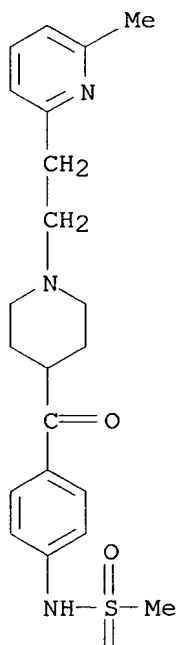
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of chronic membrane depolarization on the K⁺ channel activities in cultured rat ventricular cells)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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O

●2 HCl

L14 ANSWER 77 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:674843 HCAPLUS
DOCUMENT NUMBER: 126:47054
TITLE: Synthesis of carbon-14 labeled indolic 5HT1 receptor agonists
AUTHOR(S): Waterhouse, Ian; Cable, Karl M.; Fellows, Ian; Wipperman, Mark D.; Sutherland, Derek R.
CORPORATE SOURCE: Chem. Development Division, Glaxo Wellcome Research and Development, Stevenage, Hertfordshire, SG1 2NY, UK
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (1996), 38(11), 1021-1031
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

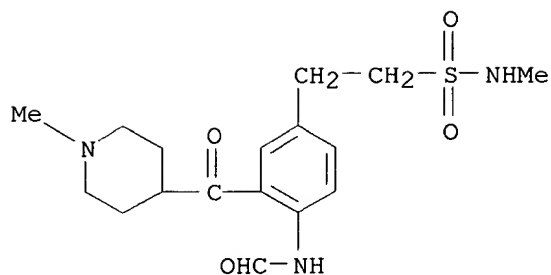
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Syntheses of carbon-14 labeled versions of indolic 5HT1, agonists sumatriptan (GR43175) (I, n = 1), GR40370 I (n = 2) and naratriptan (GR85548) (II) are described. Introduction of the label via cyanation of ketoformanilides, e.g., III, formed by oxidative cleavage of an indole ring, ensured incorporation of carbon-14 at the metabolically stable C-2 position of the indole.

IT **184646-64-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of carbon-14 labeled naratriptan, sumatriptan and analog)

RN 184646-64-8 HCAPLUS

CN Benzeneethanesulfonamide, 4-(formylamino)-N-methyl-3-[(1-methyl-4-piperidinyl)carbonyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 78 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:624637 HCAPLUS

DOCUMENT NUMBER: 125:265535

TITLE: Atrioventricular junctional rhythm induced by sympathetic stimulation in E-4031-treated dog hearts

AUTHOR(S): Imamura, Hiroshi; Furukawa, Yasuyuki; Yamazaki, Kyohei; Nakano, Hirofumi; Kasama, Miho; Hoyano, Yuji; Chiba, Shigetoshi

CORPORATE SOURCE: Dep. Pharmacol., Shinshu University Sch. Med., Matsumoto, Japan

SOURCE: Journal of Cardiovascular Pharmacology (1996), 28(4), 507-512

CODEN: JPCPDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To investigate the role of delayed rectifier potassium current (IK) on the sympathetic control of the heart, we studied the effects of E-4031, a blocker of the rapidly activating type of IK (IKr), on the chronotropic, dromotropic, and inotropic responses to sympathetic nerve stimulation in the autonomically decentralized hearts of open-chest anesthetized dogs. E-4031 (0.01-3 .mu.mol/kg i.v., i.v.) decreased the heart rate (HR) dose-dependently without affecting other cardiac functions. After E-4031 treatment, cardiac sympathetic nerve stimulation changed the sinus rhythm to the atrioventricular (AV) junctional rhythm in 6 of 11 anesthetized dogs (55%). In three of six junctional rhythm hearts, sinus rhythm supervened during sympathetic stimulation for 2 min. The no. of pacemaker shifts to junctional rhythm increased as the dose of E-4031 was increased. However, E-4031 attenuated neither the pos. chronotropic, dromotropic, nor right atrial and ventricular inotropic responses to sympathetic nerve stimulation. These results suggest that IKr inhibition may induce the AV junctional rhythm due to the combination of the different participation of IKr, the different resting potentials, and the different sensitivity to sympathetic activation among cardiac pacemaker cells.

IT 113559-13-0, E 4031

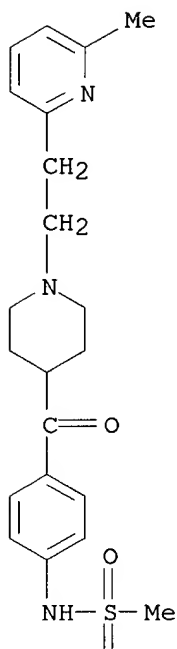
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(atrioventricular junctional rhythm induced by sympathetic stimulation in E-4031-treated dog hearts)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 79 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:579409 HCAPLUS
 DOCUMENT NUMBER: 125:292583
 TITLE: Effects of toborinone (OPC-18790), a new positive inotropic agent, on action potential in guinea pig sinoatrial node: compared with milrinone and E-4031
 AUTHOR(S): Orito, Kensuke; Takase, Hiromichi; Fujiki, Hiroyuki; Mori, Toyoki
 CORPORATE SOURCE: 2nd Tokushima Institute of New Drug Research, Otsuka Pharmaceutical Co., Ltd., Tokushima, 771-01, Japan
 SOURCE: Japanese Journal of Pharmacology (1996), 72(1), 79-82
 CODEN: JJPAAZ; ISSN: 0021-5198
 PUBLISHER: Japanese Pharmacological Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The effects of toborinone ([(+)-6-[3-(3,4-dimethoxybenzylamino)-2-hydroxypropoxy]-2(1H)-quinolinone], OPC-18790), milrinone, and E-4031 (1-(2-(6-methyl-2-pyridyl)-1-ethyl)-4-(4-methanesulfonylamino-1-

Searched by Thom Larson, STIC, 308-7309

benzoyl)piperidine dihydrochloride) on membrane potential were examd. in isolated guinea pig sinoatrial node preps. Toborinone, a new pos. inotropic agent, prolonged cycle length (CL), depolarized max. diastolic potential (MDP) and decreased max. upstroke velocity (Vmax) and action potential amplitude (APA). Milrinone, a peak III phosphodiesterase (PDE III) inhibitor, increased Vmax and APA and shortened CL and action potential duration. E-4031 an IK blocker, prolonged CL, depolarized MDP and decreased Vmax and APA. These results suggest that toborinone modulates the action potential like an IK blocker rather than a PDE III inhibitor in a sinoatrial node.

IT **113559-13-0**, E-4031

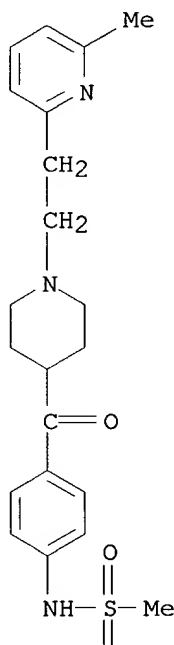
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of toborinone on action potential in guinea pig sinoatrial node in comparison with milrinone and E-4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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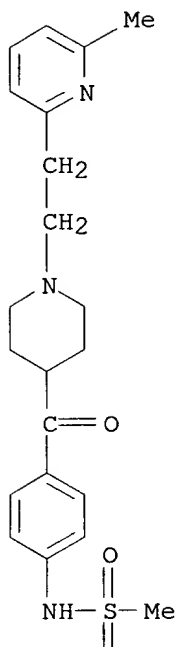
PAGE 2-A



● 2 HCl

L14 ANSWER 80 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:561380 HCAPLUS
DOCUMENT NUMBER: 125:238044
TITLE: Effects of class III antiarrhythmic drugs on the
Na+-activated K+ channels in guinea pig ventricular
cells
AUTHOR(S): Mori, Katsumi; Saito, Toshihiro; Masuda, Yoshiaki;
Nakaya, Naruaki
CORPORATE SOURCE: Dep. of Pharmacology and Third Dep. of Internal
Medicine, Chiba Univ. Sch. of Medicine, Chiba, 260,
Japan
SOURCE: British Journal of Pharmacology (1996), 119(1),
133-141
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Class III antiarrhythmic drugs are known to block the outward currents
through voltage-gated K+ channels. However, effects of class III
antiarrhythmic drugs on the ligand-gated K+ channels have not been
thoroughly examd. In this study effects of amiodarone and newer class III
antiarrhythmic drugs, E-4031 and MS-551, on the Na+-activated K+ (KNa)
current were examd. in inside-out membrane patches and in whole cells
isolated from guinea-pig ventricle. The NNa channel current was activated
by increasing [Na+]i from 0 mM to 30-100 mM with 150 mM [K+]o in
inside-out membrane patches of ventricular myocytes. The channel current
showed a larger slope conductance (210 pS), inward-going rectification and
subconductance levels of various amplitudes. E-4031 and MS-551 at high
concns. (300 .mu.M) inhibited the K+ current by decreasing the open time
(flickering block). Amiodarone at relatively low concns. (0.1-10 .mu.M)
inhibited the KNa channel current by decreasing the open probability
rather than by decreasing the open time. The IC50 value of amiodarone for
inhibiting the KNa channel current was 1.0 .mu.M. These drugs also
inhibited the whole-cell outward current activated by intracellular
loading of 50 mM [Na+]i and extracellular application of 10 .mu.M ouabain.
These results indicate that class III antiarrhythmic drugs inhibit the KNa
channel current in cardiac cells. However, there are sharp differences in
the effective concns. and the mode of inhibition between amiodarone and
the newer class III antiarrhythmic drugs.
IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(effects of class III antiarrhythmic drugs on the Na+-activated K+
channels in guinea pig ventricular cells)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 81 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:525358 HCAPLUS
DOCUMENT NUMBER: 125:191933
TITLE: Separation of the components of the delayed rectifier potassium current using selective blockers of IKr and IKs in guinea pig isolated ventricular myocytes
AUTHOR(S): Heath, B. M.; Terrar, D. A.
CORPORATE SOURCE: University Department Pharmacology, Oxford, OX1 3QT, UK
SOURCE: Experimental Physiology (1996), 81(4), 587-603
CODEN: EXPHEZ; ISSN: 0958-0670
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Delayed rectifier potassium current (IK) was investigated in guinea-pig isolated ventricular myocytes under voltage-clamp conditions ("switched" single electrode clamp), using selective blockers and/or different activation protocols to sep. its rapid (IKr) and slow (IKs) components.

Searched by Thom Larson, STIC, 308-7309

The class III antiarrhythmic compd. E4031 (5 μ M) was used to block IKr and the anesthetic drugs propofol (100 μ M) or thiopentone (100 μ M) to block IKs. In all expts. L-type calcium currents were blocked with nifedipine (2 μ M). Complementary effects of E4031 and the anesthetic drugs on the components of IK were obsd. The E4031-sensitive current (IKr) resembled the current remaining in the presence of the anesthetics and, likewise, the anesthetic-sensitive current (IKs) resembled the current remaining in the presence of E4031. Under the conditions of these expts., the relative contribution of the two components to total IK tail current was found to be approx. equal after a 400 ms depolarization to +40 mV. For example, IKr was 58 \pm 10% of total IK tail current when measured as the E4031-sensitive current, 41 \pm 6% as the propofol-insensitive current and 43 \pm 7% as the thiopentone-insensitive current. In the presence of both E4031 and propofol or thiopentone the IK tail current deactivating at -40 mV was completely eliminated, leaving a residual current during the pulse which reversed at -46 \pm 1 mV. To avoid complication of the "envelope of tails" test with this residual current, the tail: pulse ratio was calcd. for the anesthetic-sensitive component and this was const., consistent with block of a single component of IK. Forskolin (1 μ M) enhanced the current most consistent with IKs. Propofol (300 μ M) caused a 64 \pm 3% increase in action potential duration in the presence of both E4031 (5 μ M) and nifedipine (2 μ M), consistent with an important role for IKs in the repolarization of the action potential in the guinea-pig heart. The observations therefore provide further support for sep. components of IK with different characteristics in the guinea-pig heart; it appears that E4031 and propofol or thiopentone are useful complementary tools for their sepn.

IT 113559-13-0, E4031

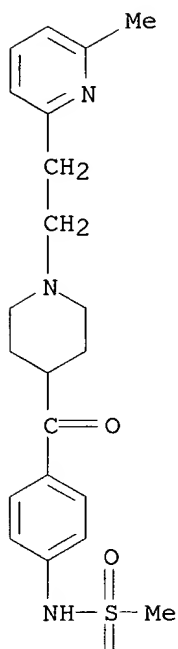
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(sepn. of the components of the delayed rectifier potassium current using selective blockers of IKr and IKs in guinea pig isolated ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 82 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:496106 HCAPLUS
DOCUMENT NUMBER: 125:158179
TITLE: Chronic in vivo and in vitro effects of amiodarone on guinea pig hearts
AUTHOR(S): Sosunov, Eugene; Anyukhovsky, Evgeny P.; Rosen, Michael R.
CORPORATE SOURCE: Coll. Physicians Surg., Columbia Univ., New York, NY, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 278(2), 906-912
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the electrophysiol. effects of chronically administered amiodarone and its interaction with a K⁺ channel blocker, amiodarone was injected i.p daily for 7 days into male guinea pigs. At 80 mg

Searched by Thom Larson, STIC, 308-7309

amiodarone/kg, RR and rate-cor. QT (QTc) intervals increased after 4 days from 209 ms and 162, resp. to 285 ms and 176, resp., and remained high on the 8th day (256 ms and 173). Twenty-four hours after the last injection, papillary muscles were isolated from both ventricles and superfused with Tyrode's soln. not contg. amiodarone. The preps. from amiodarone-treated animals manifested a prolongation of action potential duration (APD) at all pacing cycle lengths (CL) (from 300 to 1500 ms). The amiodarone-induced increase of APD diminished with elevation of K⁺ concn. Amiodarone did not modify the dependence of V_{max} on membrane potential at different K⁺ concns. There was minimal to no summation of effects of chronic amiodarone and acute superfusion of the K⁺ channel blocker E4031 (3 .times. 10⁻⁶M) on APD at CL = 1500 ms. The data demonstrate that in chronically treated guinea pigs, amiodarone prolongs repolarization, manifests min. reverse use-dependence in APD prolongation, and, at low pacing rate, shows no additive actions with an acutely superfused blocker of K⁺ channels.

IT 113559-13-0, E 4031

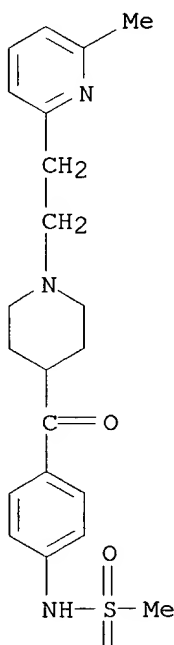
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(amiodarone effects on heart electrophysiol. response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 83 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:452766 HCAPLUS
 DOCUMENT NUMBER: 125:167962
 TITLE: Condensed thiophene compounds as D2 and 5-HT2
 antagonists and 5-HT1A agonists useful as
 antipsychotic drugs
 INVENTOR(S): Nakao, Tohru; Ono, Yuji; Bougauchi, Masahiro;
 Morimoto, Yasuto
 PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
 SOURCE: U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 107,564,
 abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|-------------------|-----------------|----------|
| US 5532240 | A | 19960702 | US 1994-272320 | 19940708 |
| CA 2104371 | AA | 19930627 | CA 1992-2104371 | 19921224 |
| US 5691330 | A | 19971125 | US 1995-478843 | 19950607 |
| PRIORITY APPLN. INFO.: | | | JP 1991-359547 | 19911226 |
| | | | JP 1992-309388 | 19921023 |
| | | | US 1993-107564 | 19930818 |
| | | | US 1994-272320 | 19940708 |
| OTHER SOURCE(S): | | MARPAT 125:167962 | | |
| GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A condensed thiophene compd. I or a pharmaceutically acceptable salt thereof, wherein ring S represents a fused thiophene ring (e.g., II); R1 represents hydrogen, halogen, alkyl, etc.; R2 represents hydrogen, alkyl, acyl, etc.; G represents CH₂, CH(OH), CO, etc.; Q represents alkylene; T represents N(Rb)(Rc) (wherein Rb, Rc represents each alkyl etc.; or alternatively Rb and Rc are combined together to form cyclic amino); D represents CH₂ or S; A and B represent each carbonyl or thiocarbonyl, or are null; and m and n represent each 0, 1 to 4, provided that m + n represents an integer of 4 or less, is useful as an antipsychotic drug having a reduced extrapyramidal side effect. Thus, e.g., 2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one (III) was prepd. by Beckmann rearrangement starting from thiophene, sulfur, and 3-bromopropionic acid; acylation of III with 4-chlorobutyryl

Searched by Thom Larson, STIC, 308-7309

chloride/ AlCl_3 afforded 7-(4-chlorobutyryl)-2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one (IV); alkylation of 4-(1,2-benzisothiazol-3-yl)piperazine hydrochloride with IV afforded 7-[4-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]butyryl]-2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one oxalate (V.oxalate). 2-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one (VI), prepd. similarly, exhibited affinities for the dopamine 2, serotonin 2, and serotonin 1A receptors of $K_i = 0.065$, 0.32, and 1.6 nM, resp., and possessed D2 antagonistic, 5-HT2 antagonistic and 5-HT1A agonistic activities according to the inhibition of apomorphine-induced hyperactivity, ergometrine-induced head-twitches and forskolin-induced adenylate cyclase activity, resp. Pharmaceutical formulations were given.

IT 169807-22-1P 169807-35-6P 169807-40-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(condensed thiophene compds. as D2 and 5-HT2 antagonists and 5-HT1A agonists useful as antipsychotic drugs)

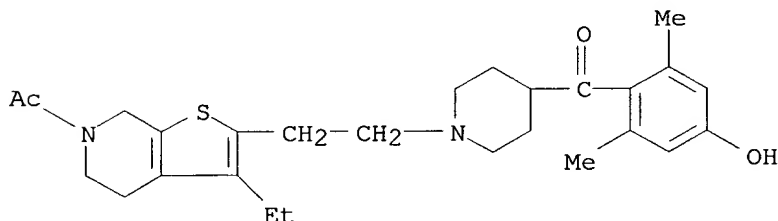
RN 169807-22-1 HCAPLUS

CN Thieno[2,3-c]pyridine, 6-acetyl-3-ethyl-4,5,6,7-tetrahydro-2-[2-[4-(4-hydroxy-2,6-dimethylbenzoyl)-1-piperidinyl]ethyl]-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 169807-21-0

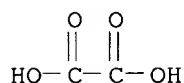
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CM 2

CRN 144-62-7

CMF C2 H2 O4

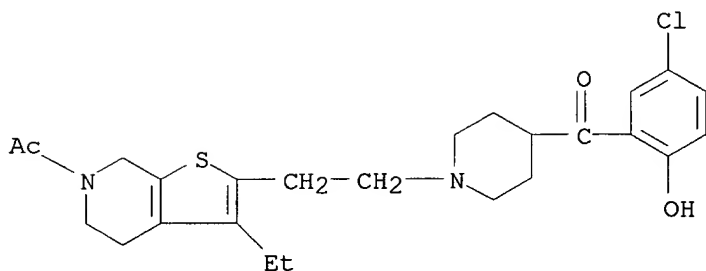


RN 169807-35-6 HCAPLUS

CN Thieno[2,3-c]pyridine, 6-acetyl-2-[2-[4-(5-chloro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-3-ethyl-4,5,6,7-tetrahydro-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

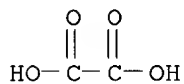
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CRN 169807-34-5
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CM 2

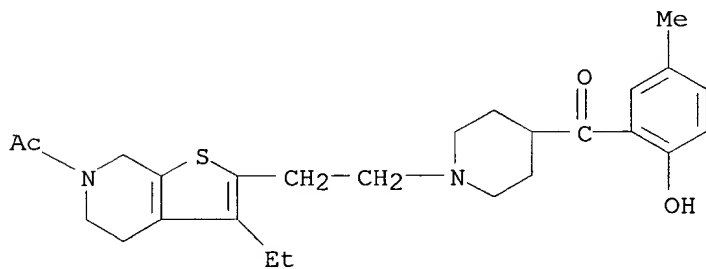
CRN 144-62-7
CMF C2 H2 O4



RN 169807-40-3 HCAPLUS
CN Thieno[2,3-c]pyridine, 6-acetyl-3-ethyl-4,5,6,7-tetrahydro-2-[2-[4-(2-hydroxy-5-methylbenzoyl)-1-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

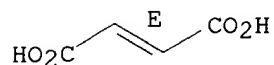
CRN 169807-39-0
CMF C26 H34 N2 O3 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



L14 ANSWER 84 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:447444 HCAPLUS

DOCUMENT NUMBER: 125:132188

TITLE: Differential effects of MS-551 and E-4031 on action potentials and the delayed rectifier K⁺ current in rabbit ventricular myocytes

AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Kodama, Itsuo; Toyama, Junji

CORPORATE SOURCE: Research Institute Environmental Medicine, Nagoya University, Nagoya, 464-01, Japan

SOURCE: Cardiovascular Research (1996), 31(6), 963-974
CODEN: CVREAU; ISSN: 0008-6363

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The frequency-dependent effects of MS-551 on the action potential duration (APD) and the underlying ionic mechanisms were investigated in comparison with those of E-4031. Whole-cell clamp techniques were used to study action potentials and ionic currents in enzymically isolated rabbit ventricular myocytes. The frequency-response obtained within the range 0.1-3.3 Hz was different for MS-551 and E-4031. The APD prolongation by MS-551 (10 μ M) was significant at 0.5-3.3 Hz, whereas that by E-4031 (1 μ M) was significant at 0.1-1.0 Hz. The prolongation by MS-551 (10 μ M) of the APD of a test action potential, which was preceded by a train of 1.0-Hz stimulation, decreased progressively as the rest duration increased, whereas that by E-4031 (1 μ M) remained at the same level. Both MS-551 (10 μ M) and E-4031 (1 μ M) decreased the delayed rectifier K⁺ current (I_K), but had no effects on the transient outward current and the inward rectifier K⁺ current. The development of the block of I_K by MS-551 and the recovery from this block were voltage dependent. At a holding potential of -50 mV, MS-551 reduced the tail current to a similar extent across all the tested durations of the depolarizing pulses to +10 mV, whereas at -75 mV, the intensity of the block progressively increased as the durations of depolarizing pulses were prolonged. The recovery from the block by MS-551 was absent at -50 mV, but occurred at -75 mV with a time const. of 577 ms. The development of the block of I_K by E-4031 was voltage and time independent. No recovery from the block by E-4031 was obsd. at either -50 or -75 mV. These findings suggest that MS-551 produces frequency-dependent class III antiarrhythmic action, presumably due to the voltage-dependent binding and unbinding to the I_K channels. The reverse frequency dependence of class III action by E-4031 cannot be explained by the effects on I_K.

IT **113559-13-0**, E 4031

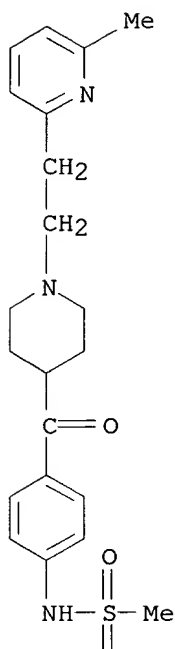
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(MS-551 and E-4031 effects on action potentials and the delayed rectifier K⁺ current in ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

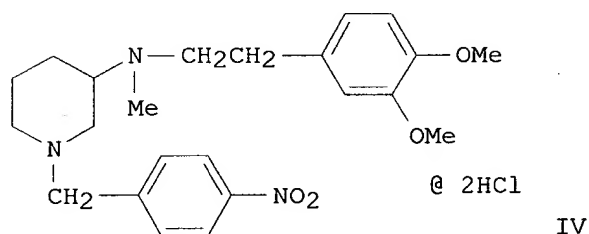
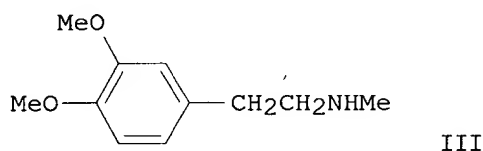
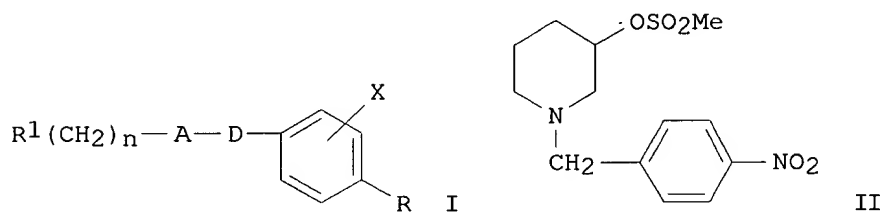
L14 ANSWER 85 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:393924 HCAPLUS
 DOCUMENT NUMBER: 125:58333
 TITLE: preparation of novel pyridine derivatives as
 antiarrhythmic agents
 INVENTOR(S): Chung, You Sup; Park, Sung Dae; Kwon, Lae Sung; Shin,
 Hong Sub; Tanabe, Shigeru
 PATENT ASSIGNEE(S): C and C Research Labs., S. Korea
 SOURCE: PCT Int. Appl., 61 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| WO 9605174 | A1 | 19960222 | WO 1995-JP1134 | 19950607 |

Searched by Thom Larson, STIC, 308-7309

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN
 RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9526296 A1 19960307 AU 1995-26296 19950607
 PRIORITY APPLN. INFO.: JP 1994-192499 19940816
 WO 1995-JP1134 19950607
 OTHER SOURCE(S): MARPAT 125:58333
 GI



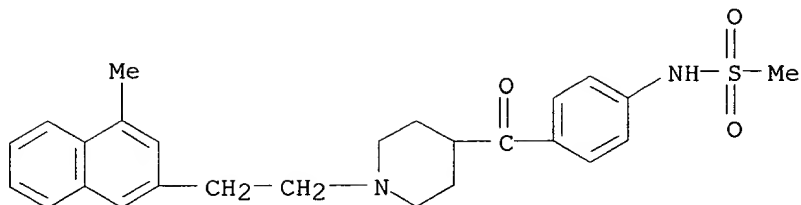
AB The title compds. [I; R = NO_2 , alkylsulfonamido; R^1 = (un)substituted Ph, quinolyl; A = 6-membered N-heterocycle residue, etc.; D = alkylene, CO, SO_2 , etc.; X = H, halo; n = 0-3], effective K channel blockers useful in treating arrhythmia with little side effects, are prepd. Reaction of 2.89 mmol mesylate (R)-II with excess amine III in MeOH and acidification with HCl gave 0.85 salt IV, which at 10^{-6} M showed an action potential duration (APD90) ratio of 108.3 at 3 Hz and 1 Hz, vs. 37.6 with a ref. compd., in an elec. stimulation test of ventricular muscle fiber.

IT **178244-84-3P 178244-85-4P 178245-09-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of novel pyridine derivs. as antiarrhythmic agents)

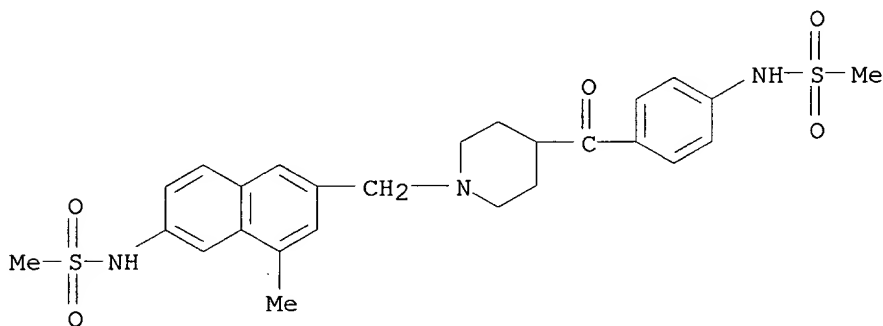
RN 178244-84-3 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-methyl-2-naphthalenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



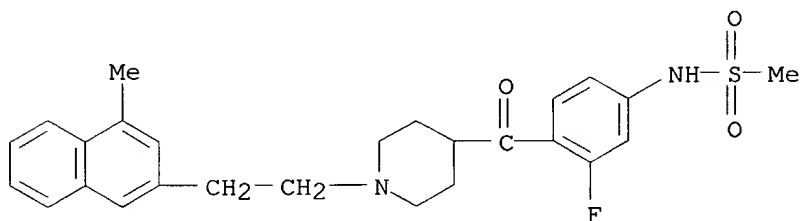
RN 178244-85-4 HCAPLUS

CN Methanesulfonamide, N-[8-methyl-6-[[4-[4-[(methanesulfonyl)amino]benzoyl]-1-piperidinyl]methyl]-2-naphthalenyl]- (9CI) (CA INDEX NAME)



RN 178245-09-5 HCAPLUS

CN Methanesulfonamide, N-[3-fluoro-4-[[1-[2-(4-methyl-2-naphthalenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 86 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:329481 HCAPLUS

DOCUMENT NUMBER: 125:25910

TITLE: Properties of E-4031-induced early afterdepolarizations in rabbit ventricular myocytes: Studies using a perforated patch method

AUTHOR(S): Zhou, Zhengfeng; Studenik, Christian; January, Craig T.

CORPORATE SOURCE: University Chicago, Chicago, IL, USA

SOURCE: Potassium Channels in Normal and Pathological Conditions (1995), 375-378. Editor(s): Vereecke, Johan; Van Bogaert, Pierre-Paul; Verdonck, Fons. Leuven University Press: Louvain, Belg.

CODEN: 62WUAM

Searched by Thom Larson, STIC, 308-7309

DOCUMENT TYPE: Conference

LANGUAGE: English

AB In the present study, the authors report the application of the perforated patch clamp method to study the role of intracellular calcium and calcium channels in E-4031-induced early afterdepolarizations.

IT **113559-13-0**, E-4031

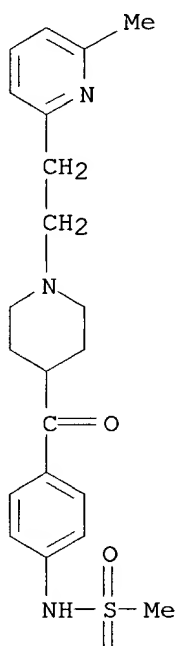
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(properties of E-4031-induced early afterdepolarizations in rabbit ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 87 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:267009 HCAPLUS

DOCUMENT NUMBER: 124:332491

Searched by Thom Larson, STIC, 308-7309

TITLE: Differential blocking properties of the new class-III antiarrhythmic agents, MS-551 and E-4031, on the cardiac delayed rectifier K⁺ current

AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Kodama, Itsuo; Toyama, Junji

CORPORATE SOURCE: Research Institute of Environmental Medicine, Nagoya University, Nagoya, 464-01, Japan

SOURCE: Environmental Medicine (1995), 39(2), 137-40
CODEN: ENMEE9; ISSN: 0287-0517

PUBLISHER: Nagoya University, Research Institute of Environmental Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

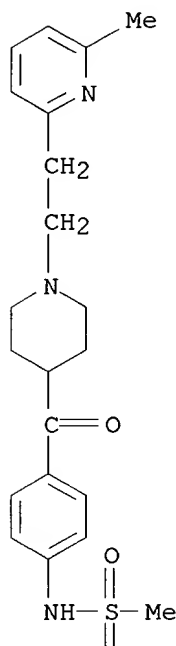
AB The effects of MS-551 and E-4031 on the delayed rectifier K⁺ currents (IK) were comparatively investigated in rabbit ventricular myocytes. Both MS-551 (10 μ M) and E-4031 (1 μ M) decreased IK to the same extent at all depolarizing levels tested without altering the voltage dependence of activation. Development of the block on IK and its recovery by MS-551 (3 μ M) were voltage dependent. At a holding potential of -75 mV, the intensity of the block progressively increased as the depolarizing durations were prolonged. Recovery was rapid with a time const. of 577. \pm .179 ms. Development of the block on IK by E-4031 (0.3 μ M) was voltage independent. No recovery was obsd. for E-4031 (0.3 μ M) at either holding potential -50 mV or -75 mV. These findings suggest that frequency-dependent prolongation in the action potential duration (APD) by MS-551 is due to voltage-dependent binding to the IK channels, but that the reverse use dependency of E-4031 cannot be explained by analyzing the effects on IK.

IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential blocking properties of the new class-III antiarrhythmic agents, MS-551 and E-4031, on the cardiac delayed rectifier K⁺ current)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 88 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:267004 HCAPLUS
DOCUMENT NUMBER: 124:331746
TITLE: Sympathetic beta-adrenoceptor stimulation in cardiac muscle treated with class-III antiarrhythmic agents
AUTHOR(S): Kodama, Itsuo; Suzuki, Ryoko; Toyama, Junji
CORPORATE SOURCE: Research Institute of Environmental Medicine, Nagoya University, Nagoya, 464-01, Japan
SOURCE: Environmental Medicine (1995), 39(1), 65-8
CODEN: ENMEE9; ISSN: 0287-0517
PUBLISHER: Nagoya University, Research Institute of Environmental Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of cardiac beta stimulation during treatment with Class-III antiarrhythmic drugs were investigated in isolated rabbit ventricular muscles. Addnl. application of isoproterenol (Isp 0.1 .mu.M) to preps. pretreated with E-4031 (0.3 .mu.M) caused a shortening in the action

Searched by Thom Larson, STIC, 308-7309

potential duration (APD) and an increase in the contractile force. The Isp actions were characterized by enhanced neg. deflection (dip) in the early repolarization phase, and induction of marked APD alternation. Most of these Isp actions were suppressed by ryanodine, a specific inhibitor of Ca²⁺ handling by the sarcoplasmic reticulum (SR). These findings suggest that activation of the Ca²⁺-sensitive transient outward current (I_{to2}) may play an important role for proarrhythmias of sympathetic stimulation in the hearts under treatment with Class-III drugs.

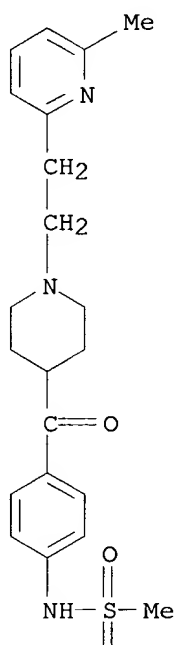
IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(sympathetic beta-adrenoceptor stimulation in cardiac muscle treated with class-III antiarrhythmic agents)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 89 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:249836 HCAPLUS

DOCUMENT NUMBER: 124:332414

TITLE: Hypotonic-induced stretch counteracts the efficacy of the class III antiarrhythmic agent E-4031 in guinea pig myocytes

AUTHOR(S): Groh, William J.; Gibson, Kevin J.; Maylie, James G.

CORPORATE SOURCE: Department of Medicine, Oregon Health Sciences University, Portland, OR, 97201-3098, USA

SOURCE: Cardiovascular Research (1996), 31(2), 237-45

CODEN: CVREAU; ISSN: 0008-6363

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim was to det. the effect and mechanisms by which myocyte stretch interacts with the prolongation of action potential duration (APD) by the class III antiarrhythmic agent E-4031. Action potentials and whole-cell currents were measured in isolated guinea pig ventricular myocytes with a patch clamp procedure during perfusion of normotonic, normotonic with addn. of E-4031, and hypotonic plus E-4031 solns. Cell swelling leading to membrane stretch of myocytes in the whole-cell recording configuration occurred with hypotonic soln. perfusion. APD, prolonged by E-4031, was reduced to less than control value with hypotonic-induced stretch. Evaluation of whole-cell currents after hypotonic-induced stretch revealed no significant changes in the L-type Ca²⁺ current, inward rectifier K⁺ current or the rapid component of the delayed rectifier K⁺ current. The slow component of the delayed rectifier K⁺ current (IKs) was upregulated and a stretch-induced Cl⁻ current was activated in hypotonic solns. The hypotonic-induced modulation of these currents was not effected by protein kinase A or C inhibition. Hypotonic-induced stretch shortens APD and counteracts the effects of E-4031. This APD shortening is secondary to upregulation of IKs and activation of a stretch-induced Cl⁻ current.

IT 113559-13-0, E-4031

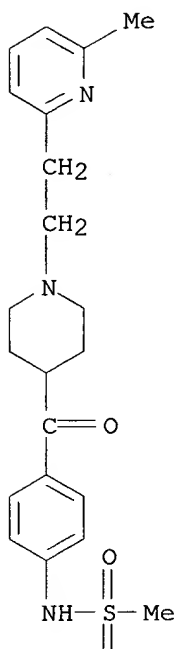
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(hypotonic-induced stretch counteracts the efficacy of the class III antiarrhythmic agent E-4031 in guinea pig myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 90 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:170350 HCAPLUS
 DOCUMENT NUMBER: 124:250394
 TITLE: Intracellular [Mg⁺⁺] determines specificity of K⁺ channel block by a class III antiarrhythmic drug
 AUTHOR(S): Sudo, Gisele Zapata; Sanguinetti, Michael C.
 CORPORATE SOURCE: Dep. Pharmacology, Merck Research Lab., West Point, PA, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 276(3), 951-7
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB E-4031 and related methanesulfonanilide class III antiarrhythmic drugs block IKr, a cardiac delayed rectifier K⁺ current. The current-voltage relation of IKr exhibits rectification; currents progressively decline in magnitude at test potentials >0 mV. Whole-cell voltage-clamp techniques

Searched by Thom Larson, STIC, 308-7309

were used to determine whether rectification results from block of channels by intracellular Mg^{++} . The properties of E-4031-sensitive current were compared in guinea pig ventricular myocytes internally perfused with either a nominally Mg^{++} -free solution or with a solution containing 1 mM Mg^{++} . Based on an envelope of tails test, we conclude that inward rectification of guinea pig IK_r is due to a voltage-dependent gating mechanism and does not result from block of the channel by intracellular Mg^{++} . Under normal physiological conditions, E-4031 is a specific blocker of IK_r . However, in the absence of intracellular Mg^{++} , E-4031 also partially blocks IK_s . Block of IK_s is prevented by prior treatment of cells with isoproterenol, which suggests that E-4031 only blocks unphosphorylated IK_s channels in the absence of intracellular Mg^{++} .

IT **113559-13-0**, E-4031

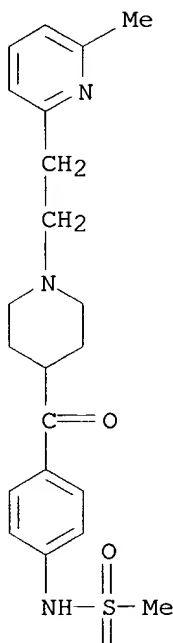
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(intracellular $[Mg^{++}]$ determines specificity of K^+ channel block by a class III antiarrhythmic drug)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



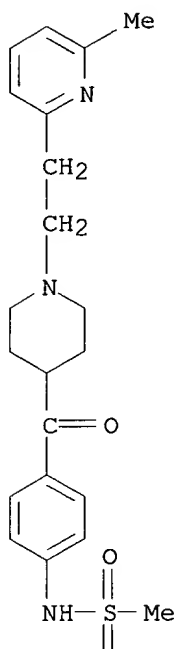
PAGE 2-A

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●2 HCl

L14 ANSWER 91 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:159636 HCAPLUS
DOCUMENT NUMBER: 124:250337
TITLE: Effect of E-4031 on QT dispersion and its modification
by isoproterenol in a 7-day-old canine model of
myocardial infarction
AUTHOR(S): Ogawa, S.; Mitamura, H.; Tsutsumi, N.; Yoshimoto, T.;
Sueyosi, K.; Takatsuki, S.; Sibata, M.
CORPORATE SOURCE: School Medicine, Keio University, Tokyo, Japan
SOURCE: Recent Progress in Electropharmacology of the Heart,
Proceedings of the International Satellite Symposium
of the 59th Annual Scientific Meeting of the Japanese
Circulation Society, Nagoya, Apr. 3-4, 1995 (1996),
Meeting Date 1995, 169-76. Editor(s): Toyama, Junji;
Hiraoka, Masayasu; Kodama, Itsuo. CRC: Boca Raton,
Fla.
CODEN: 62LYAD
DOCUMENT TYPE: Conference
LANGUAGE: English
AB E-4031 prolonged the QT intervals with a decrease of QT in the epicardial
border zone of 7-day-old canine model of myocardial infarction. The
degree of QT prolongation was inversely related to the baseline QT
intervals. Isoproterenol partially reversed the effects of E-4031 on QT
intervals, QT dispersion and arrhythmogenesis. The results are discussed
in relation to whether the antiarrhythmic activity of E-4031 can be
decreased by .beta.-adrenergic stimulation.
IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(effect of E-4031 on QT dispersion and modification by isoproterenol in
a 7-day-old canine model of myocardial infarction in relation to
.beta.-adrenergic stimulation)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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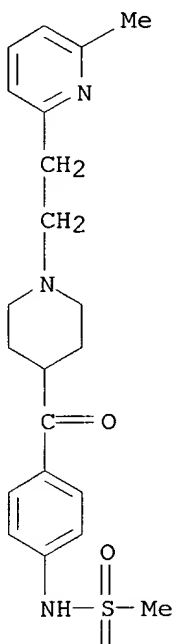
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L14 ANSWER 92 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:159623 HCAPLUS
DOCUMENT NUMBER: 124:278496
TITLE: Selective inhibition by IF inhibitors of increases in
sinus rate induced by sympathetic interventions in the
heart
AUTHOR(S): Furukawa, Y.; Chiba, S.
CORPORATE SOURCE: School Medicine, Shinshu University, Matsumoto, Japan
SOURCE: Recent Progress in Electropharmacology of the Heart,
Proceedings of the International Satellite Symposium
of the 59th Annual Scientific Meeting of the Japanese
Circulation Society, Nagoya, Apr. 3-4, 1995 (1996),
Meeting Date 1995, 27-36. Editor(s): Toyama, Junji;
Hiraoka, Masayasu; Kodama, Itsuo. CRC: Boca Raton,
Fla.
CODEN: 62LYAD
DOCUMENT TYPE: Conference
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

- AB In dogs, the blocker of the activated inward current (IF) zatebradine inhibited the pos. chronotropic response to sympathetic nerve activation without affecting other pos. cardiac responses, whereas the verapamil and E-4031 did not have selective activity on heart rate. In isolated dog atria, the order of the selective inhibition by bradycardic agents of the pos. chronotropic response to norepinephrine was zatebradine = E-4080 > alinidine > falipamil. Expts. were done which suggested that zatebradine selectively inhibits the pos. chronotropic response to cAMP-related cardiotonic agents in dog heart. An IF inhibitor may be a clin. useful bradycardic agents for treatment of sinus tachycardia.
- IT **113559-13-0**, E-4031
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (selective inhibition by activated inward current (IF) inhibitor zatebradine and other bradycardic agents of increases in sinus rate induced by sympathetic stimulation in heart)
- RN 113559-13-0 HCAPLUS
- CN Methanesulfonamide, N-[4-[[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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●2 HCl

L14 ANSWER 93 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:131858 HCAPLUS
DOCUMENT NUMBER: 124:220034
TITLE: Class III antiarrhythmic drugs block HERG, a human
cardiac delayed rectifier K⁺ channel: open-channel
block by methanesulfonanilides
AUTHOR(S): Spector, Peter S.; Curran, Mark E.; Keating, Mark T.;
Sanguinetti, Michael C.
CORPORATE SOURCE: Dep. Human Genetics, Univ. Utah Health Sci. Cent.,
Salt Lake City, UT, USA
SOURCE: Circulation Research (1996), 78(3), 499-503
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

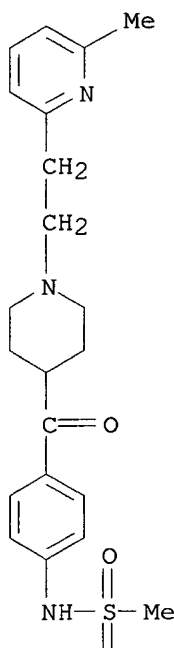
AB The authors recently reported that mutations in HERG, a potassium channel gene, cause long QT syndrome. Heterologous expression of HERG in *Xenopus* oocytes revealed that this channel had biophys. properties nearly identical to a cardiac delayed rectifier K⁺ current, I_{Kr}, but had dissimilar pharmacol. properties. Class III antiarrhythmic drugs such as E-4031 and MK-499 are potent and specific blockers of I_{Kr} in cardiac myocytes. The authors initial studies indicated that these compds. did not block HERG at a concn. of 1 $\mu\text{mol/L}$. In the present study, the authors used std. two-microelectrode voltage-clamp techniques to further characterize the effects of these drugs on HERG channels expressed in oocytes. Consistent with initial findings, 1 $\mu\text{mol/L}$ MK-499 and E-4031 had no effect on HERG when oocytes were voltage clamped at a neg. potential and not pulsed during equilibration with the drug. However, MK-499 did block HERG current if oocytes were repetitively pulsed, or clamped at a voltage pos. to the threshold potential for channel activation. This finding is in contrast to previous studies that showed significant block of I_{Kr} in isolated myocytes by similar drugs, even in the absence of pulsing. This apparent discrepancy may be due to differences in channel characteristics (HERG vs. guinea pig and mouse I_{Kr}), tissue (oocytes vs. myocytes), or specific drugs. Under steady state conditions, block of HERG by MK-499 was half maximal at 123 nmol/L at a test potential of -20 mV. MK-499 (150 nmol/L) did not affect the voltage dependence of activation and rectification nor the kinetics of activation and rectification nor the kinetics of activation and deactivation of HERG. These data indicate that MK-499 preferentially blocks open HERG channels and further support the conclusion that HERG subunits form I_{Kr} channels in cardiac myocytes.

IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(class III antiarrhythmic methanesulfonanilides block human cardiac delayed rectifier K⁺ channel HERG by open-channel block)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 94 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:131353 HCAPLUS
DOCUMENT NUMBER: 124:220033
TITLE: Negative chronotropic and dromotropic effects of E-4031, an IKr blocker, on the atrioventricular node in anesthetized dog hearts
AUTHOR(S): Yamazaki, Kyouhei; Furukawa, Yasuyuki; Kasama, Miho; Imamura, Hiroshi; Chiba, Shigetoshi
CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, Matsumoto, 390, Japan
SOURCE: European Journal of Pharmacology (1996), 297(3), 233-9
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English

AB To investigate the effect of the delayed rectifier K⁺ current (IK) on the atrioventricular (AV) node of the heart in situ, the authors studied the direct effects of 1-[2-(6-methyl-2-pyridyl)ethyl]-4-(methylsulfonyl-aminobenzoyl)piperidine (E-4031), an IKr (a rapid type of IK) blocker, on the AV junctional rate, atrio-His interval (AH interval), and right ventricular pressure, and the cardiac responses to sympathetic nerve stimulation in the anesthetized dog heart. AV junctional rhythm was induced by clamping the sinoatrial (SA) pacemaker area. E-4031 (0.01-3 .mu.mol/kg, i.v.) attenuated the AV junctional rate dose dependently. The junctional neg. chronotropic effect was less than the decrease in sinus rate induced by E-4031 in the same doses. E-4031 did not affect the junctional rate increased by sympathetic stimulation. In the paced heart, E-4031 slightly increased the AH interval but did not change right ventricular pressure responses. E-4031 attenuated neither pos. dromotropic nor pos. ventricular pressure responses to sympathetic stimulation. After E-4031 treatment, zatebradine (a hyperpolarization-activated current blocker) additively decreased the junctional rate and the junctional pos. chronotropic responses to sympathetic stimulation. These results suggest that IKr has much less effect on AV nodal pacemaker activity than on SA nodal pacemaker activity, and an IKr blocker, E-4031, unlike zatebradine, does not antagonize the junctional pos. chronotropic responses to sympathetic activation in anesthetized dog heart.

IT 113559-13-0, E-4031

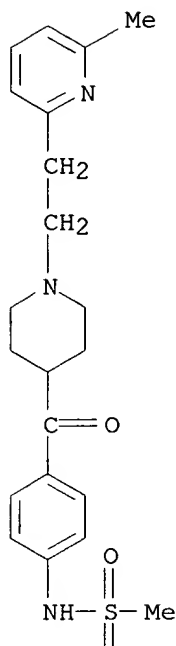
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(neg. chronotropic and dromotropic effects of blocker of delayed rectifier potassium current E-4031 on atrioventricular node in anesthetized dog hearts in relation to zatebradine)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 95 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:121765 HCAPLUS
DOCUMENT NUMBER: 124:219948
TITLE: Inhibition of potassium currents by the antiarrhythmic drug E4031 in rat taste receptor cells
AUTHOR(S): Sun, Xiao-Dong; Herness, M. Scott
CORPORATE SOURCE: Indiana University School of Medicine, Center for Medical Education, Ball State University, Muncie, IN, 47306, USA
SOURCE: Neuroscience Letters (1996), 204(3), 149-52
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of the class III antiarrhythmic agent E4031 was investigated on a non-cardiac prepn. as a potential tool for studying potassium currents. Patch clamp recordings in the whole cell configuration were performed on

Searched by Thom Larson, STIC, 308-7309

dissoecd. rat taste cells. These cells possess a variety of potassium currents; they also conduct action potentials. Unlike its more specific action on a type of delayed rectifier channel in cardiac cells, three types of potassium currents were reversibly diminished in taste cells in the presence of E4031. These included transient, sustained, and inwardly-rectifying potassium currents. Activation properties were not altered but the inactivation curve was shifted to the left by approx. 10 mV. Inhibitions of whole cell currents were voltage-dependent, larger at depolarized potentials, but were never complete. E4031 significantly broadened the gustatory action potential and, at higher concns., inhibited spike height, suggesting an addnl. inhibitory effect on sodium channels that was evident in voltage-clamp records. We conclude that E4031 is an effective inhibitor of potassium currents in the micromolar range and that it likely acts at a conserved segment of the potassium channel.

IT **113559-13-0**, E4031

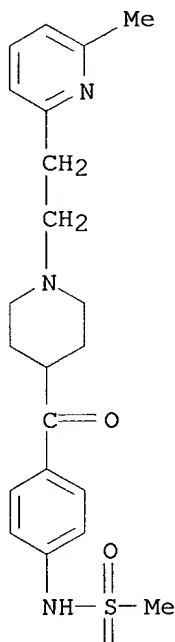
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(antiarrhythmic E4031 inhibition of potassium currents in taste receptor cells in relation to use as tool for potassium channel study)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 96 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:112731 HCAPLUS

DOCUMENT NUMBER: 124:219905

TITLE: Selective inhibition by a class III antiarrhythmic agent, E-4031, of the negative chronotropic response to parasympathetic stimulation in anesthetized dogs

AUTHOR(S): Imamura, Hiroshi; Furukawa, Yasuyuki; Nakano, Hirofumi; Kasama, Miho; Hoyano, Yuji; Chiba, Shigetoshi

CORPORATE SOURCE: Department of Pharmacology, Shinshu University School of Medicine, matsumoto, 390, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 276(2), 467-72

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To investigate the influence of a class III antiarrhythmic agent, E-4031, on the vagus control of the heart, we studied the effects of E-4031 on the chronotropic, dromotropic and inotropic responses to parasympathetic stimulation in the autonomically decentralized hearts of the open-chest, anesthetized dogs. E-4031 (0.01-3 $\mu\text{mol/kg}$ i.v.) decreased heart rate dose-dependently without affecting atrioventricular (AV) conduction time, first deriv. of "a" wave component of the right atrial pressure (RA dP/dt), max. rate of the right ventricular pressure developed (RV + dP/dt) and arterial blood pressure. When cervical vagus stimulation decreased the heart rate, RA dP/dt and RV + dP/dt and prolonged the AV conduction time, E-4031 antagonized the neg. chronotropic response in a dose-dependent manner but affected neither dromotropic nor atrial inotropic responses. E-4031 at a high dose of 3 $\mu\text{mol/kg}$ i.v. attenuated the ventricular inotropic response. ID50 for the chroniotropism was 0.20 $\mu\text{mol/kg}$. Stimulation of the selective intracardiac parasympathetic nerves to the sinoatrial nodal area decreased the heart rate of RA dP/dt without a dromotropic response. E-4031 antagonized the neg. chronotropic response to the stimulation but not the inotropic response. E-4031 antagonized the neg. chronotropic response to the stimulation but not the inotropic response. Stimulation of the selective intracardiac parasympathetic nerves to the AV nodal area prolonged the AV conduction time without a chronotropic response. E-4031 at a high dose of 3 $\mu\text{mol/kg}$ i.v. attenuated the neg. dromotropic response to the stimulation by 35%. These results suggest that E-4031 preferentially blocks the neg. chronotropic response to vagus stimulation without significantly affecting other cardiac responses at a site distal to the muscarinic receptor in the heart in situ.

IT 113559-13-0, E-4031

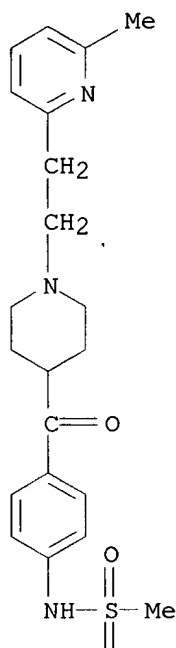
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(inhibition of neg. chronotropic response to parasympathetic stimulation by class III antiarrhythmic agent E-4031 in anesthetized dogs)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 97 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:107309 HCAPLUS
 DOCUMENT NUMBER: 124:193865
 TITLE: Assessment of reverse use-dependent blocking actions of class III antiarrhythmic drugs by 24-hour holter electrocardiography
 AUTHOR(S): Okada, Yutaka; Ogawa, Satoshi; Sadanga, Tsuneaki; Mitamura, Hideo
 CORPORATE SOURCE: School Medicine, Keio University, Tokyo, 108, Japan
 SOURCE: Journal of the American College of Cardiology (1996), 27(1), 84-9

Searched by Thom Larson, STIC, 308-7309

CODEN: JACCDI; ISSN: 0735-1097

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This clin. study was designed to compare rate-dependent effects of class III agents on QT prolongation. Clin. data that compare the electrophysiol. differences among class III agents with different selectivity for potassium channels are still lacking. QT intervals were measured over a wide range of preceding RR intervals during sinus rhythm by 24-h Holter electrocardiog. before and after oral administration of four class III agents: E4031, dofetilide, MS551 and d-sotalol. Rate-dependent changes in the QT interval were assessed by the slope of the linear regression line estg. the QT-/RR relation. All agents significantly increased the mean slope: E4031 increased the mean [+-SD] value from 0.32 +- 0.05 to 0.42 +- 0.13 ($p < 0.01$), dofetilide from 0.32 +- 0.03 to 0.50 +- 0.12 ($p < 0.03$), MS551 from 0.35 +- 0.06 to 0.45 +- 0.10 ($p < 0.02$) and d-sotalol from 0.31 +- 0.05 to 0.33 +- 0.04 ($p < 0.05$). However, in those patients given either E4031, dofetilide or MS551, the degree of QT prolongation was smaller at shorter /RR intervals and was better preserved at shorter /RR intervals by d-sotalol, with a smaller increase in slope ($p < 0.02$ vs. dofetilide and MS551). On ambulatory electrocardiog., reverse use dependence in QT prolongation was least prominent with d-sotalol among the four study drugs. In the range of physiol. heart rates, class III agents could manifest different profiles of rate dependence in their QT-prolonging effect.

IT 113559-13-0, E4031

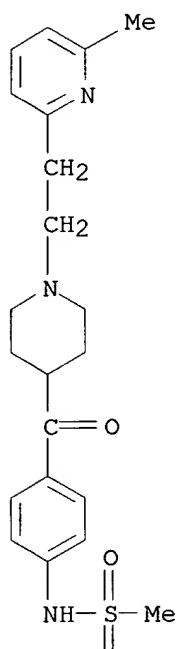
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(assessment of reverse use-dependent blocking actions of class III antiarrhythmic drugs by 24-h holter electrocardiog. in humans)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 98 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:96793 HCAPLUS
DOCUMENT NUMBER: 124:164847
TITLE: Effect of the class III antiarrhythmic agent E-4031 on the ATP-sensitive potassium channel in rabbit ventricular myocytes
AUTHOR(S): West, Paul D.; Bursill, Jane A.; Wyse, Kenenth R.; Martin, Donald K.; Campbell, Terence J.
CORPORATE SOURCE: Dep. Cardiology, St. Vincent's Hosp., Sydney, 2010, Australia
SOURCE: Pharmacology & Toxicology (Copenhagen) (1996), 78(2), 89-93
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The class III antiarrhythmic drug E-4031, a known blocker of the delayed rectifier potassium channel (IK), might also be capable of blocking the

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ATP-sensitive potassium channel (IKATP). The authors examd. this possibility by studying the effect of E-4031 on single IKATP channels in membrane patches excised from ventricular myocytes that were obtained by std. enzymic disocn. techniques from New Zealand white rabbits. In inside-out patches, E-4031 caused a dose-dependent block of IKATP with an EC50 of 31 .mu.M, Hill coeff. of 0.89 and no effect on channel conductance. Open dwell-time kinetics were fitted by two exponential components, with E-4031 causing redn. of the longer time const. In outside-out patches, the concn. of E-4031 required to produce blockade was much higher. The authors conclude that E-4031 blocks the ATP-sensitive potassium channel and that it does so from within the cytoplasm, with one-to-one channel binding stoichiometry. Single channel conductance is unchanged, but the longer time const. for the open state is reduced, which suggests that E-4031 may be an open channel blocker of intermediate to slow time course.

IT **113559-13-0**, E-4031

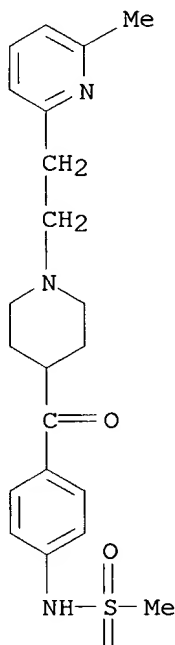
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of the class III antiarrhythmic agent E-4031 on the ATP-sensitive potassium channel in rabbit ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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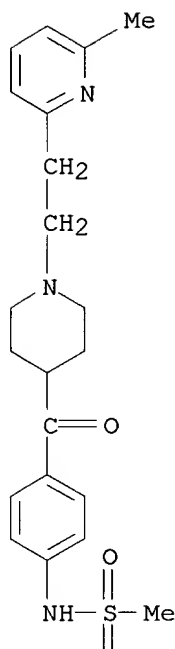
PAGE 2-A

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L14 ANSWER 99 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:28724 HCAPLUS
DOCUMENT NUMBER: 124:106114
TITLE: Comparison of direct negative chronotropic and
positive inotropic effects of sematilide to those of
E-4031 and MS-551 and the reverse frequency-dependent
prolongation of cardiac refractoriness of sematilide
AUTHOR(S): Yamada, Akio; Motomura, Shigeru; Hashimoto, Keitaro
CORPORATE SOURCE: Dep. Pharmacology, Yamanashi Medical Univ., Yamanashi,
Japan
SOURCE: Journal of Cardiovascular Pharmacology (1996), 27(1),
159-66
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Direct cardiac effects of sematilide, a new class II antiarrhythmic drug,
were compared with those of E-4031 and MS-551 in canine isolated
blood-perfused heart preps. Doses of sematilide, E-4031, and MS-551
causing a 10% decrease in the spontaneous sinoatrial beating rate were 58,
9, and 84 .mu.g; those causing a 10% increase in developed tension of the
papillary muscle were 485, 17, and 267 .mu.g; and those causing a 10%
prolongation of effective refractory period (ERP) of the atrioventricular
node were 68, 11, and 53 .mu.g, resp. There were few effects on atrio-His
or His-ventricular intervals. Also, in in situ open-chest dog hearts, the
percent increases in ERP of the atrioventricular conduction system caused
by 1 mg/kg of sematilide were 21, 16 and 9% at cycle lengths of 800, 600,
and 400 ms, resp. These results indicate that (a) sematilide, as well as
E-4031 and MS-551, has direct neg. chronotropic and pos. inotropic effects
and prolongs cardiac refractoriness without affecting conduction velocities;
(b) quant., the cardiac effects of sematilide were almost identical to
those of MS-551 and five to ten times less potent than those of E-4031;
(c) and prolongation of ERP of the atrioventricular conduction system by
sematilide occurred in a reverse frequency-dependent manner.
IT 113559-13-0, E-4031
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(comparison of direct neg. chronotropic and pos. inotropic effects of
sematilide to those of E-4031 and MS-551 and the reverse
frequency-dependent prolongation of cardiac refractoriness of
sematilide)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 100 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996:5064 HCAPLUS
 DOCUMENT NUMBER: 124:106039
 TITLE: Two components of delayed rectifier current in canine atrium and ventricle. Does IKs play a role in the reverse rate dependence of class III agents?
 AUTHOR(S): Gintant, Gary A.
 CORPORATE SOURCE: Masonic Medical Research Laboratory, Utica, NY, USA
 SOURCE: Circulation Research (1996), 78(1), 26-37
 CODEN: CIRUAL; ISSN: 0009-7330
 PUBLISHER: American Heart Association
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Because the no. and characteristics of delayed rectifier K⁺ current (IK) components vary between species, the role of each component in the action potential and modulation by class III agents is uncertain. To address these issues, IK was assessed in adult isolated canine ventricular and atrial myocytes by using whole-cell and perforated-patch techniques. IK

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components were characterized by using two complementary approaches: a kinetic approach (based on biexponential fits to deactivating tail currents) and a pharmacol. approach (using the methanesulfonanilide compd. E-4031). In ventricular myocytes, two exponential tail current components were distinguished; these components differed in the voltage and time dependence of activation and the effect of lower $[K^+]_o$. Both kinetic components contributed equally to peak tail current amplitude (measured at -35 mV) after a single 300-ms pulse to 5 mV, simulating an action potential. By use of E-4031, rapidly and slowly activating components of IK (IKr and IKs, resp.) that were analogous to tail components described kinetically were identified. The activation kinetics and rectification properties of canine IKr and IKs are qual. similar to those described previously for guinea pigs. In contrast, canine IKr and IKs deactivation kinetics differed markedly from those found in guinea pigs, with canine IKr deactivating slowly (time const. τ , 2 to 3 s near -35 mV) and IKs deactivating rapidly (τ , 150 ms near -35 mV and decreasing to 30 ms near -85 mV). E-4031 elicited reverse rate-dependent effects (greater drug-induced prolongation of the action potential at slower stimulation rates); this effect is inconsistent with the hypothesis attributing reverse rate dependence to incomplete IKs deactivation during rapid stimulation (due to rapid deactivation of canine IKs). Two IK components with characteristics comparable to those found in ventricular myocytes were also obsd. in atrial myocytes. In conclusion, (1) IKr- and IKs-like components of IK are present in canine atrial and ventricular myocytes, with deactivation kinetics strikingly different from those found in guinea pigs, and (2) the rapid deactivation kinetics of canine IKs do not support its role in reverse rate dependence with class III agents in this species.

IT 113559-13-0, E-4031

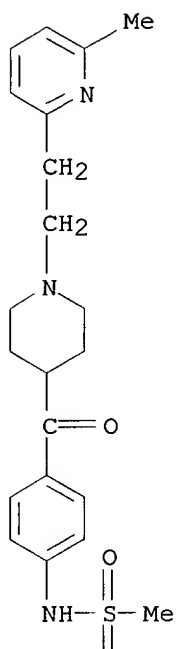
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(two components of delayed rectifier current in canine atrium and ventricle in relation to reverse rate dependence of class III antiarrhythmic agents)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 101 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1995:982514 HCAPLUS
 DOCUMENT NUMBER: 124:15496
 TITLE: Pharmaceutical composition containing a class III antiarrhythmic agent and a class IV antiarrhythmic agent
 INVENTOR(S): Bril, Antoine Michel Alain; Faivre, Jean-Francois Simon Pierre; Gout, Bernard Emile Joseph; Forest, Marie-Claire
 PATENT ASSIGNEE(S): SmithKline Beecham Laboratories Pharmaceutiques, Fr.
 SOURCE: PCT Int. Appl., 36 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

Searched by Thom Larson, STIC, 308-7309

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|--|----|----------|----------------|----------|
| WO 9526726 | A1 | 19951012 | WO 1995-EP1165 | 19950328 |
| W: JP, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 752859 | A1 | 19970115 | EP 1995-914321 | 19950328 |
| R: BE, CH, DE, FR, GB, IT, LI, NL | | | | |
| JP 09510985 | T2 | 19971104 | JP 1995-525402 | 19950328 |
| PRIORITY APPLN. INFO.: | | | GB 1994-6479 | 19940331 |
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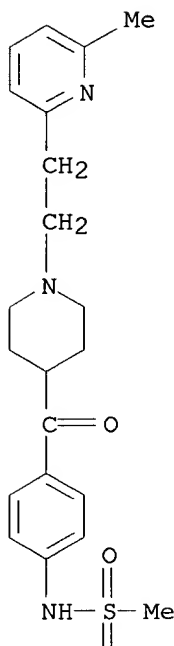
AB A pharmaceutical compn.with improved antiarrhythmic activity and a reduced adverse effect profile comprises a class III antiarrhythmic agent (generally a K channel blocker) and a class IV antiarrhythmic agent (generally a Ca channel blocker), providing that the compn. is not a combination of 10 .mu.g E4031/kg and 0.1 mg verapamil/kg, and optionally a pharmaceutically acceptable carrier. The class III agent is present in an antiarrhythmically effective amt. and the class IV agent is present in an amt. lower than that which provides a substantial Ca-blocking effect. Thus, in dogs with myocardial infarction and elec.-induced ventricular arrhythmia, a combination of verapamil (0.03 mg/kg i.v.) and E4031 (0.1 mg/kg i.v.) completely suppressed arrhythmia; at higher doses of verapamil, the occurrence of conduction block led to adverse effects.

IT **113559-13-0**, E 4031
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antiarrhythmic compn. contg. class III and class IV antiarrhythmic agents)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 102 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:915127 HCAPLUS
DOCUMENT NUMBER: 123:305992
TITLE: Comparative Evaluation of the Predictive Power of
Calculation Procedures for Molecular Lipophilicity
AUTHOR(S): Mannhold, Raimund; Rekker, Roelof F.; Sonntag,
Christoph; Ter Laak, Anton M.; Dross, Karl;
Polymeropoulos, Emmanuel E.
CORPORATE SOURCE: Department of Lasermedicine, Heinrich-Heine-
Universitaet, Duesseldorf, 40225, Germany
SOURCE: J. Pharm. Sci. (1995), 84(12), 1410-19
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The predictive power of four calcn. procedures for mol. lipophilicity is
checked by comparing with exptl. data (log P and chromatog. RMw) taken
from the literature. Two sets of test compds. are used: the first
comprises simple org. mols. and the second consists of more complicated

drug mols. Our comparative evaluation leads us to conclude that the predictive power is significantly better for not too complicated org. mols. than for drugs with complicated structural pattern. The four investigated calcn. procedures should be arranged in two groups with significantly differing predictive power: (a) Rekker and Hansch/Leo and (b) Ghose/Crippen and Suzuki/Kudo. This conclusion is based on a statistical control using log P and RMw as the independent parameters. Correlations have in common: (1) slopes in correlations with calcd. data based on fragmental methods are not significantly different from 1; calcns. with data from atom-based procedures show up in most cases with slopes below 1. (2) The accompanying overall statistics underline the superiority of the fragmental methods. We think that all four tested calcn. procedures have their own restrictions; for future development we would advise a thorough reconsideration of structural effects not fully (or even not at all) incorporated in the data sets. Special attention will have to be paid to the conformational aspects of lipophilic behavior.

IT 113559-13-0, E 4031

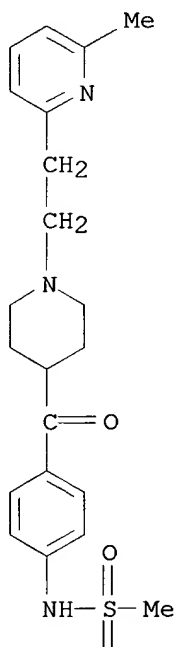
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparative evaluation of the predictive power of calcn. procedures for mol. lipophilicity)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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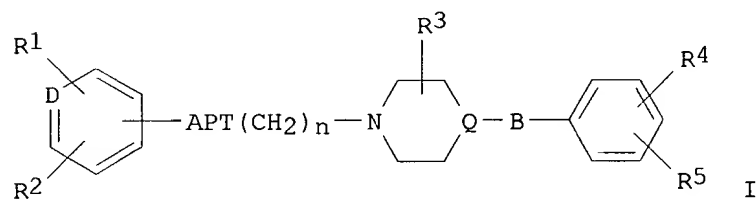


● 2 HCl

L14 ANSWER 103 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1995:902630 HCAPLUS
 DOCUMENT NUMBER: 123:313770
 TITLE: Preparation of piperidino and piperazino 5-HT₂ receptor antagonists and blood platelet aggregation inhibitors
 INVENTOR(S): Aoki, Tsuyoshi; Takahashi, Atsuo; Sato, Hiroyasu; Shimanuki, Eiichi; Gengyou, Kaoru; Nishimata, Toyoki; Ishigami, Sachiko; Yamada, Shin-ichi; Yamaguchi, Takahiro; et al.
 PATENT ASSIGNEE(S): Toa Eiyo Ltd., Japan
 SOURCE: Eur. Pat. Appl., 123 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|-------------------|-----------------|----------|
| EP 661266 | A1 | 19950705 | EP 1994-120698 | 19941227 |
| R: BE, CH, DE, ES, FR, GB, IT, LI, LU, NL | | | | |
| JP 07242629 | A2 | 19950919 | JP 1994-336707 | 19941226 |
| PRIORITY APPLN. INFO.: | | | JP 1993-346805 | 19931227 |
| OTHER SOURCE(S): | | MARPAT 123:313770 | | |

GI



AB The title compds. [I; A = CH₂, CO, sulfonyl; B, T = direct bond, CH₂, CO, CH(OH), C(:NH); D = CH, N, N.fwdarw.O; P = N, N.fwdarw.O; Q = CH, N; R₁, R₂ = H, OH, (un)branched alkyl, alkenyl, (un)substituted aralkyl, acyl, (un)substituted NH₂, etc.; R₃ = H, OH, (un)branched alkyl or alkoxy; R₄, R₅ = H, OH, halogen, (un)branched alkyl, alkenyl, alkoxy, alkylthio, (un)substituted NH₂, SH, etc.; n = 1-6], useful as 5-HT₂ receptor antagonists and blood platelet aggregation inhibitors, are prepd. Thus, 4-acetylamino-N-[2-[4-(4-fluorobenzoyl)piperidino]ethyl]-N-(3-methoxyphenyl)benzamide fumarate, m.p. 215-222.degree. (decompn.), prepd.

by the reaction of the free base with fumaric acid, demonstrated a IC50 for platelet aggregation in rabbit-derived, platelet-rich plasma of .ltoreq.9.9 x 10-8 M, vs. 1.0-9.9 x 10-7 M for ketanserin.

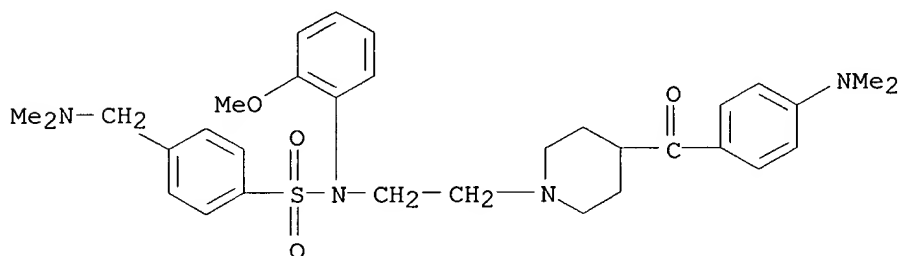
IT 169948-15-6P 169948-16-7P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of piperidino and piperazino 5-HT2 receptor antagonists and blood platelet aggregation inhibitors)

RN 169948-15-6 HCAPLUS

CN Benzenesulfonamide, N-[2-[4-[4-(dimethylamino)benzoyl]-1-piperidinyl]ethyl]-4-[(dimethylamino)methyl]-N-(2-methoxyphenyl)- (9CI)
(CA INDEX NAME)



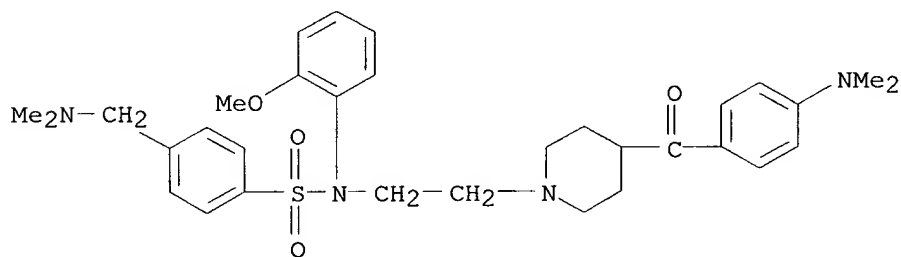
RN 169948-16-7 HCAPLUS

CN Benzenesulfonamide, N-[2-[4-[4-(dimethylamino)benzoyl]-1-piperidinyl]ethyl]-4-[(dimethylamino)methyl]-N-(2-methoxyphenyl)-, ethanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 169948-15-6

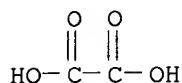
CMF C32 H42 N4 O4 S



CM 2

CRN 144-62-7

CMF C2 H2 O4



L14 ANSWER 104 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:898442 HCAPLUS

DOCUMENT NUMBER: 123:310993

TITLE: A quantitative description of the E-4031-sensitive

repolarization current in rabbit ventricular myocytes

AUTHOR(S): Clay, John R.; Ogbaghebriel, Azieb; Paquette, Tyna;

Sasyniuk, Betty I.; Shrier, Alvin

CORPORATE SOURCE: Natl. Inst. Neurological Disorders Stroke, Natl. Inst.

Health, Bethesda, MD, 20897, USA

SOURCE: Biophys. J. (1995), 69(5), 1830-7

CODEN: BIOJAU; ISSN: 0006-3495

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have measured the E-4031-sensitive repolarization current (IKr) in single ventricular myocytes isolated from rabbit hearts. The primary goal of this anal. was a description of the IKr kinetic and ion transfer properties. Surprisingly, the max. time const. of this component was 0.8 s at 33-34.degree., which is significantly greater than the value of 0.18 s previously reported under similar conditions in the original measurements of IKr from guinea pig ventricular myocytes. The primary, novel feature of the anal. concerns the relation of the bell-shaped curve that describes the voltage dependence of the kinetics and the sigmoidal curve that describes the activation of IKr. The midpoint of the latter occurred at approx. +10 mV on the voltage axis, as compared to -30 mV for the point on the voltage axis at which the max. time const. occurred. Moreover, the voltage dependence of the kinetics was much broader than the steepness of the activation curve would predict. Taken together, these results comprise a gating current paradox that is not resolved by the incorporation of a fast inactivated state in the anal. The fully activated current-voltage relation for IKr exhibited strong inward-going rectification, so much so that the current was essentially nil at +30 mV, even though the channel opens rapidly in this voltage range. This result is consistent with the lack of effect of E-4031 on the early part of the plateau phase of the action potential. Surprisingly, the reversal potential of IKr was .apprx.15 mV pos. to the potassium ion equil. potential, which indicates that this channel carries inward current during the latter part of the repolarization phase of the action potential.

IT 113559-13-0, E-4031

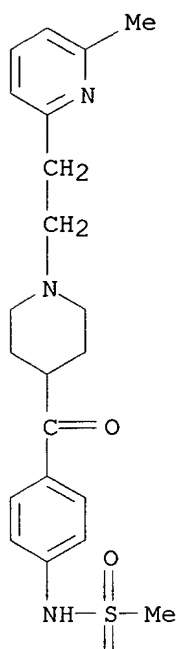
RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)

(E-4031-sensitive potassium transport by heart ventricle)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 105 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:896104 HCAPLUS
DOCUMENT NUMBER: 123:314031
TITLE: Preparation of fused thiophene derivatives with high
affinity to dopamine D2 and serotonin 2 (5-HT2)
receptors
INVENTOR(S): Nakao, Tatsu; Ono, Juji; Bogauchi, Masahiro; Morimoto,
Yasuto
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 78 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|-------|-----------------|-------|
| ----- | ---- | ----- | ----- | ----- |

Searched by Thom Larson, STIC, 308-7309

JP 07070135 A2 19950314 JP 1994-143144 19940624
 JP 2959615 B2 19991006
 PRIORITY APPLN. INFO.: JP 1993-179837 19930624
 OTHER SOURCE(S): MARPAT 123:314031
 GI For diagram(s), see printed CA Issue.
 AB Thieno[3,2-b]azepin-5-one derivs. and analogs [I; ring S = fused thiophene Q1 - Q4; R1 = H, halo, alkyl, acyl, hydroxyalkyl; R2 = H, alkyl, acyl, aryl, arylalkyl; wherein G = CH₂, CH(OR₃) (wherein R₃ = H, alkyl, acyl), CO, S(O)t (wherein t = 0-2); Q = linear or branched alkylene; T = tert-amino; D = CH₂, S(O)u (u = 0-2); when m = 0 or 1 and n = 0-2, one of A and B is absent and the other represents CO or C(S); or when m, n = 0-4, both A and B is absent; provided that m + n .ltoreq.4], which are both antagonists of dopamine D2 receptors and blockers of serotonin 2 (5-HT₂) receptor, are useful as psychotropic agents with reduced side effects such hormonal and extrapyramidal side effects and excellent stability in blood, and effective for improving both pos. and neg. symptoms of schizophrenia, are prepd. Thus, 2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one (II; R1 = H) (prepn. given) was acylated by chlorobutyryl chloride in the presence of AlCl₃ in CH₂Cl₂ under ice-cooling to give, after recrystn. from EtOH, II [R1 = CO(CH₂)₃Cl] which was condensed with 4-(1,2-benzisothiazol-3-yl)piperazine hydrochloride in the presence of K₂CO₃ and KI in DMF/toluene at 100.degree. for 24 h to give, after silica gel chromatog. and salt formation with oxalic acid, II (R1 = Q5) oxalate. A thieno[2,3-c]pyridine deriv. (III) showed binding affinity to dopamine D2 receptor prepn. from synaptosome of Wister rat corpus striatum with Ki value of 0.15 nM and binding affinity to serotonin 2 (5-HT₂) receptor and serotonin 1A (5-HT_{1A}) receptor prepn. from synaptosome of Wister rat hippocampus with Ki value of 0.043 and 3.7 nM, resp. These title compds. I in vivo also antagonized the effects of apomorphine and ergometrine in rats.

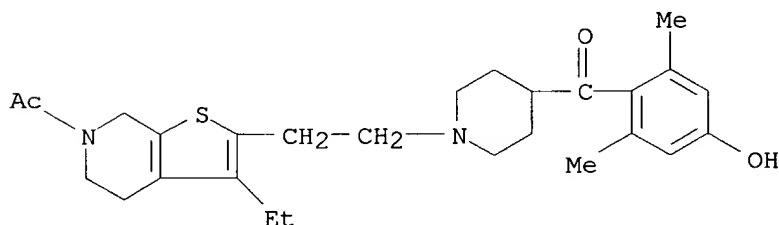
IT **169807-22-1P 169807-35-6P 169807-40-3P**
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of fused thiophene derivs. with high affinity to dopamine D2 and serotonin 2 (5-HT₂) receptors as psychotropic agents)

RN 169807-22-1 HCAPLUS
 CN Thieno[2,3-c]pyridine, 6-acetyl-3-ethyl-4,5,6,7-tetrahydro-2-[2-[4-(4-hydroxy-2,6-dimethylbenzoyl)-1-piperidinyl]ethyl]-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

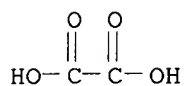
CRN 169807-21-0

CMF C27 H36 N2 O3 S



CM 2

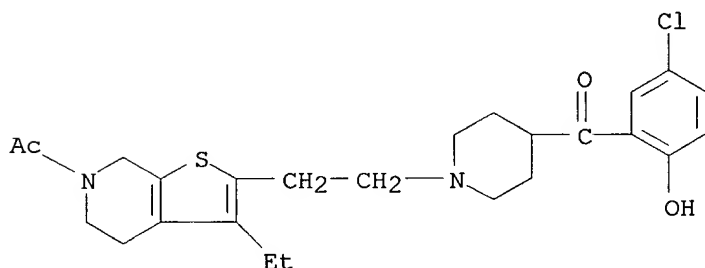
CRN 144-62-7
CMF C2 H2 O4



RN 169807-35-6 HCAPLUS
CN Thieno[2,3-c]pyridine, 6-acetyl-2-[2-[4-(5-chloro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-3-ethyl-4,5,6,7-tetrahydro-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

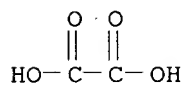
CM 1

CRN 169807-34-5
CMF C25 H31 Cl N2 O3 S



CM 2

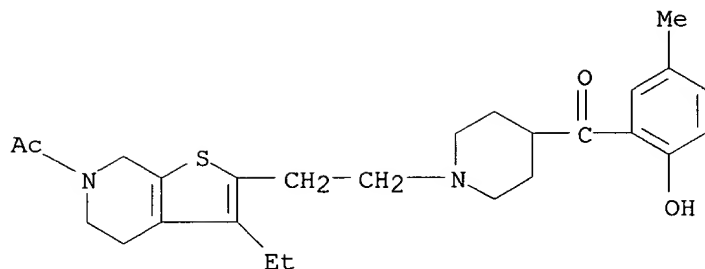
CRN 144-62-7
CMF C2 H2 O4



RN 169807-40-3 HCAPLUS
CN Thieno[2,3-c]pyridine, 6-acetyl-3-ethyl-4,5,6,7-tetrahydro-2-[2-[4-(2-hydroxy-5-methylbenzoyl)-1-piperidinyl]ethyl]-, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 169807-39-0
CMF C26 H34 N2 O3 S



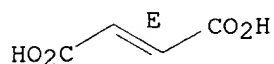
CM 2

CRN 110-17-8

CMF C4 H4 O4

CDES 2:E

Double bond geometry as shown.



L14 ANSWER 106 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:821494 HCAPLUS

DOCUMENT NUMBER: 123:305855

TITLE: Application of hyphenated LC/NMR and LC/MS techniques in rapid identification of in vitro and in vivo metabolites of iloperidone

AUTHOR(S): Mutlib, A. E.; Strupczewski, J. T.; Chesson, S. M.

CORPORATE SOURCE: Neuroscience Product Group Unit, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ, 08876, USA

SOURCE: Drug Metab. Dispos. (1995), 23(9), 951-64

CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Iloperidone, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone, is currently undergoing clin. trails as a potential antipsychotic agent. Iloperidone was extensively metabolized to a no. of metabolites by rats, dogs, and humans, LC/MS/MS was used to characterize and identify metabolites of iloperidone present in complex biol. mixts. obtained from all three species. Identification of some of the unknown metabolites in rat bile was achieved successfully by combination of LC/NMR and LC/MS with a min. amt. of sample cleanup. The utility of coupling a semipreparative HPLC to LC/MS instrument for further characterization of collected metabolites was demonstrated. It was shown that iloperidone was metabolized by O-dealkylation processes to yield 6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole and 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-hydroxyphenyl]ethanone. Oxidative N-dealkylation led to the formation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole and a secondary metabolite, 3-[(4-acetyl-2-methoxy)phenoxy]propionic acid. Iloperidone was reduced to produce 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-.alpha.-methylbenzenemethanol as the major metabolite in humans and rats.

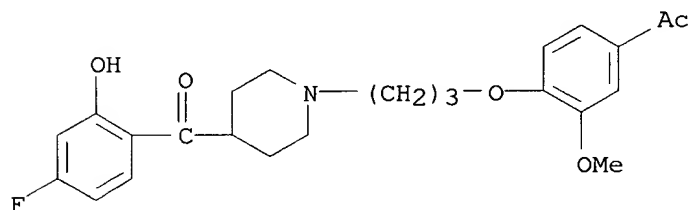
Hydroxylation of iloperidone produced 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-hydroxy-5-methoxyphenyl]ethanone and 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methoxyphenyl]propoxy]-2-hydroxyethanone, the later of which was the principal metabolite in dogs. The identities of all these metabolites were established by comparing the LC/MS retention times and mass spectral data with synthetic stds.

IT **170170-50-0**

RL: ANT (Analyte); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)
(liq. chromatog. and mass spectroscopy identification of iloperidone metabolites in humans and lab. animals)

RN 170170-50-0 HCAPLUS

CN Ethanone, 1-[4-[3-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]propoxy]-3-methoxyphenyl]- (9CI) (CA INDEX NAME)

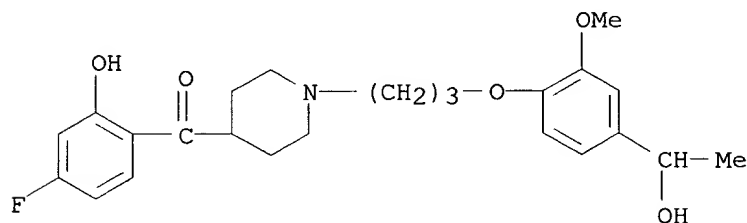


IT **170170-53-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(liq. chromatog. and mass spectroscopy identification of iloperidone metabolites in humans and lab. animals)

RN 170170-53-3 HCAPLUS

CN Methanone, (4-fluoro-2-hydroxyphenyl)[1-[3-[4-(1-hydroxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 107 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:660106 HCAPLUS

DOCUMENT NUMBER: 123:102340

TITLE: Anticholinergic effects of class III antiarrhythmic drugs in guinea pig atrial cells: different molecular mechanisms

AUTHOR(S): Mori, Katsumi; Hara, Yukio; Saito, Toshihiro; Masuda, Yoshiaki; Nakaya, Haruaki

CORPORATE SOURCE: School of Medicine, Chiba University, Chiba, 260, Japan

SOURCE: Circulation (1995), 91(11), 2834-43
CODEN: CIRCAZ; ISSN: 0009-7322

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It is well known that vagal stimulation increases the vulnerability to atrial fibrillation via muscarinic receptor-mediated shortening of refractory period. Recently it has been reported that some class III antiarrhythmic drugs effectively terminate or prevent atrial flutter and fibrillation by prolonging atrial effective refractory period. However, effects of class III antiarrhythmic drugs on the muscarinic acetylcholine receptor-operated K⁺ current (IK.ACh), which is important for the repolarization phase of the action potential in atrial cells, have not been thoroughly examd. Effects of three class III antiarrhythmic drugs, dl-sotalol, E-4031, and MS-551, on the carbachol (1 .mu.mol/L)-induced action potential shortening and outward K⁺ current were examd. in guinea pig atrial cells by conventional microelectrode and patch clamp techniques. In isolated left atrial dl-sotalol (100 .mu.mol/L), E-4031 (3 .mu.mol/L), and MS-551 (30 .mu.mol/L) partially reversed the carbachol-induced action potential shortening. In isolated single atrial cells, IK.ACh was activated by extracellular application of carbachol (1 .mu.mol/L) or adenosine (10 .mu.mol/L) or by intracellular loading of GTP.gamma.S (100 .mu.mol/L). Sotalol (3 to 1000 .mu.mol/L), E-4031 (1 to 100 .mu.mol/L), and MS-551 (1 to 100 .mu.mol/L) inhibited the carbachol-induced IK.ACh in a concn.-dependent manner, and their IC50 (half-maximal inhibition) values were 35.5, 7.8, and 11.4 .mu.mol/L, resp. However, the GTP.gamma.S-induced and adenosine-induced IK.ACh were inhibited by high concns. of E-4031 and MS-551 but not by sotalol. Sotalol may inhibit IK.ACh by the blockade of the atrial muscarinic receptors, whereas E-4031 and MS-551 may inhibit the current not only by blocking the muscarinic receptors but also by depressing the function of the K⁺ channel itself and/or G proteins. These drugs may potentially be useful for the prevention and termination of atrial flutter and fibrillation through their inhibitory action on IK.ACh.

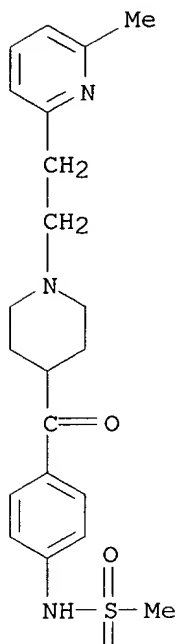
IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)(class III antiarrhythmic drugs inhibition of muscarinic
receptor-operated potassium current in anticholinergic effects in,
atrial cells)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 108 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:644378 HCAPLUS
DOCUMENT NUMBER: 123:102357
TITLE: Electrophysiological effect of BRL-32872, a novel antiarrhythmic agent with potassium and calcium channel blocking properties, in guinea pig cardiac isolated preparations
AUTHOR(S): Bril, Antoine; Faivre, Jean-Francois; Forest, Marie-Claire; Cheval, Brigitte; Gout, Bernard; Linee, Philippe; Ruffolo, Robert R., Jr.; Poyser, Robert H.
CORPORATE SOURCE: SmithKline Beecham Laboratories Pharmaceutiques, Saint-Gregoire, Fr.
SOURCE: J. Pharmacol. Exp. Ther. (1995), 273(3), 1264-72
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of N-(3,4-dimethoxyphenyl)-N-3-[[2-(3,4-dimethoxyphenyl) ethyl] propyl]-4-nitrobenzamide hydrochloride (BRL-32872), a novel antiarrhythmic

Searched by Thom Larson, STIC, 308-7309

agent, were studied in guinea pig cardiac prepn. using std. microelectrode and patch-clamp techniques. In papillary muscle, BRL-32872 did not change resting membrane potential and max. rate of depolarization but prolonged action potential duration (APD) by 24% at 1.0 μM . When the concn. was increased to 3.0 and 10.0 μM , the effect on APD was not further enhanced, and a bell-shaped dose-response curve resulted. Patch-clamp expts. in isolated myocytes showed that BRL-32872 inhibited the rapidly activating component of the delayed rectifier potassium current ($\text{EC}_{50} = 0.028 \mu\text{M}$) and the L-type calcium current ($\text{EC}_{50} = 2.8 \mu\text{M}$) but had a limited effect on the inward rectifier potassium current. In papillary muscles stimulated at 300, 500, 1000 and 2000 ms, the effect of BRL-32872 in prolonging APD did not vary. By contrast, N-(4-(1-[2-(6-methyl-2-pyridyl)ethyl]-4-piperidyl)carbonylphenyl)methanesulfonamide dihydrochloride dihydrate (E-4031), a pure class III antiarrhythmic agent, increased APD more at slower than at faster stimulation rates, which illustrated the reverse frequency-dependence of this agent. Among the 35 expts. performed with BRL-32872, only one fiber showed early afterdepolarizations (EADs), and these, which occurred at 1.0 μM , were suppressed at higher concn. (3.0 μM). Moreover, EADs induced by E-4031 were suppressed by BRL-32872 (3.0 μM). BRL-32872, which inhibits the rapidly activating component of the delayed rectifier potassium current and the L-type calcium current, may represent a novel treatment of cardiac arrhythmias. That BRL-32872 may show a low incidence of adverse effects is suggested by the lack of reverse frequency-dependent effect on APD, the relative absence of EADs and the ability to antagonize EADs produced by typical class III antiarrhythmic agents.

IT 113559-13-0, E-4031

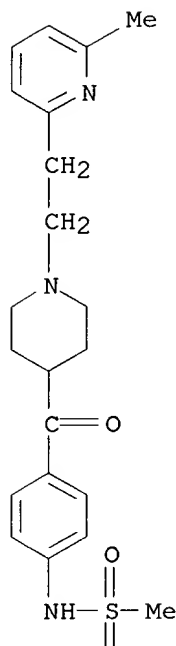
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(heart electrophysiol. effects of antiarrhythmic BRL-32872 comparison with E4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 109 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:527717 HCAPLUS
DOCUMENT NUMBER: 122:306192
TITLE: Evidence for multiple antiarrhythmic binding sites on the cardiac rapidly activating delayed rectifier K⁺ channel
AUTHOR(S): Chadwick, Christopher C.; Krafte, Douglas S.; O'Connor, Bernard; Volberg, Walter A.; Ezrin, Alan M.; Johnson, Robert E.; Silver, Paul J.
CORPORATE SOURCE: Departments of Pharmacology and Medicinal Chemistry, Sterling Winthrop Pharmaceutical Research Division, Collegeville, PA, USA
SOURCE: Drug Dev. Res. (1995), 34(4), 376-80
CODEN: DDREDK; ISSN: 0272-4391
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have previously shown that [3H]dofetilide binds with high affinity to sites assocd. with the guinea pig cardiac rapidly activating delayed

Searched by Thom Larson, STIC, 308-7309

rectifier K⁺ (IKr) channel and that class III antiarrhythmic agents, including dofetilide, clofilium, quinidine, sotalol, and sematilide, competitively displace [3H]dofetilide with IC₅₀ values that correlate with those for blockade of the IKr channel. In this report, we show that other class III antiarrhythmic agents, namely, E-4031 (1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methylsulfonylamidobenzoyl)piperidine) and L-691,121 (3,4-dihydro-1'-[2-(benzofurazan-5-yl)ethyl]-6-methanesulfonamidospiro[(2H)-1-benzopyran-2,4'-piperidin]-4-one), potently block guinea pig IKr channels with resp. IC₅₀ values of 29 and 8 nM, yet have a low potency for displacement of [3H]dofetilide. Moreover, WIN 61773-2 [(R)(+)-4,5-dihydro-4-methyl-1-phenyl-3(2-phenylethyl)-(1H)-2,4-benzodiazepine monohydrochloride] biphasically displaces [3H]dofetilide according to a two site competitive binding model (site 1 = 21% displacement, IC₅₀ = 116 nM; site 2 = 79% displacement, IC₅₀ = 50 .mu.M) with correlation to IKr block in the first phase (IC₅₀ = 92 nM). These findings suggest that E-4031, L-691,121, and WIN 61773-2 inhibit IKr channels by interacting at sites distinct from the high affinity [3H]dofetilide binding site. The partial displacement of [3H]dofetilide by low concns. of WIN 61773-2, correlated with complete block of IKr, suggests allosteric modulation of the dofetilide binding site by this agent.

IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); THU

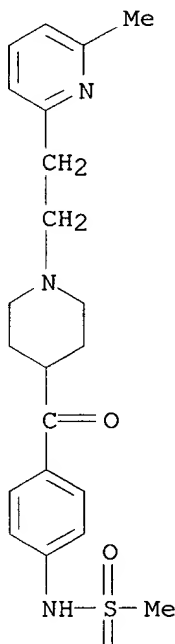
(Therapeutic use); BIOL (Biological study); USES (Uses)

(evidence for multiple antiarrhythmic binding sites on cardiac rapidly activating delayed rectifier K⁺ channel)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



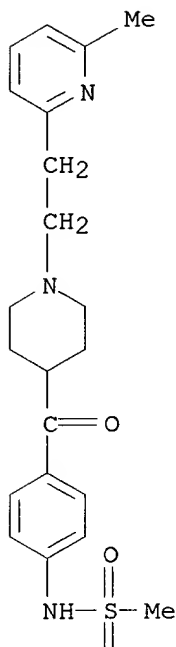
PAGE 2-A

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●2 HCl

L14 ANSWER 110 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:430363 HCAPLUS
DOCUMENT NUMBER: 122:204308
TITLE: A review of the effects of three cardioactive agents
on the electrical activity from embryonic chick heart
cell aggregates: TTX, ACh, and E-4031
AUTHOR(S): Clay, John R.; Kristof, Arnold S.; Shenasa, Jafar;
Brochu, Richard M.; Shrier, Alvin
CORPORATE SOURCE: National Institute Neurological Disorders and Stroke,
National Institutes Health, Bethesda, MD, 20892, USA
SOURCE: Prog. Biophys. Mol. Biol. (1994), 62(3), 185-202
CODEN: PBIMAC; ISSN: 0079-6107
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with refs. The effects of tetrodotoxin (TTX), acetylcholine
(ACh), and E-4031 on the elec. activity from the embryonic chick heart
cell are discussed cardiotoxic.
IT **113559-13-0**, E-4031
RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)
(cardioactive agents effect on elec. activity from embryonic chick
heart cell aggregates)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 111 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1995:408232 HCAPLUS
 DOCUMENT NUMBER: 122:178038
 TITLE: Effect of isoproterenol on facilitation of electrical
 defibrillation by E-4031
 AUTHOR(S): Sezaki, Kazunori; Murakawa, Yuji; Inoue, Hiroshi;
 Nakajima, Toshiaki; Usui, Masahiro; Yamashita,
 Takeshi; Ajiki, Kohsuke; Oikawa, Naoki; Iwasawa,
 Kuniaki; Omata, Masao
 CORPORATE SOURCE: 2nd Dep. Internal Med., Univ. Tokyo, Tokyo, Japan
 SOURCE: J. Cardiovasc. Pharmacol. (1995), 25(3), 393-6
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB To det. whether isoproterenol could reverse enhancement of elec.
 defibrillation effectiveness by class III antiarrhythmic agents, the
 authors measured the internal defibrillation threshold (DFT) in 12
 anesthetized dogs during infusion of (a) saline (baseline), (b)

Searched by Thom Larson, STIC, 308-7309

isoproterenol, (c) isoproterenol + E4031 (a new class III antiarrhythmic agent), and (d) E4031 alone. The isoproterenol infusion was adjusted so that heart rate (HR) was at least 30 beats/min greater than baseline. E4031 was given as a 40-.mu.g/kg bolus at the beginning of the third stage of the study, followed by const. infusion at 2 .mu.g/kg/min. Eight dogs completed the study. Although the energy-based DFT was not affected by isoproterenol (from 6.1 to 6.0 J), it was decreased to 3.7 J in the third stage by infusion of E4031 and isoproterenol. After the discontinuation of isoproterenol in the fourth stage, i.e., during infusion of E4031 alone, DFT was 3.4 J. Therefore, isoproterenol did not antagonize the effect of E4031 on the DFT, suggesting the possible clin. usefulness of class III agents for facilitating defibrillation even in the presence of augmented sympathetic activity.

IT **113559-13-0**, E-4031

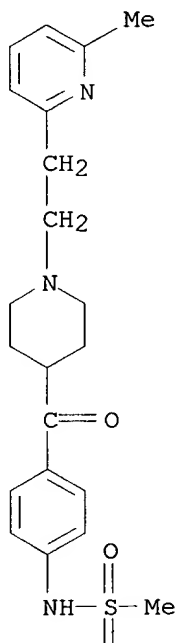
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of isoproterenol on facilitation of elec. defibrillation by
class III antiarrhythmic E-4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

L14 ANSWER 112 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:326891 HCAPLUS

DOCUMENT NUMBER: 122:96146

TITLE: Comparison of binding to rapidly activating delayed rectifier K⁺ channel, IKr, and effects on myocardial refractoriness for class III antiarrhythmic agents

AUTHOR(S): Lynch, Joseph J., Jr.; Baskin, Elizabeth P.; Nutt, Elka M.; Guinosso, Peter J., Jr.; Hamill, Terence; Salata, Joseph J.; Woods, Catherine M.

CORPORATE SOURCE: Dep. Pharmacology Radiopharmacology, Merck Res. Lab., West Point, PA, USA

SOURCE: J. Cardiovasc. Pharmacol. (1995), 25(2), 336-40

CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Satn. binding studies in guinea pig ventricular myocytes with 3H-dofetilide, a radioligand for the cardiac rapidly activating delayed rectifier K⁺ IKr channel, indicated specific high-affinity binding with a K_d of 83 nM and a B_{max} of 0.18 pmol/mg cellular protein (1.36 x 10⁶ sites/cell). Using displacement of high-affinity 3H-dofetilide binding as a measure of interaction with the IKr channel, potencies (K_i values) for binding to the IKr channel in guinea pig myocytes for six class III antiarrhythmic agents were characterized and compared to indexes of functional electrophysiol. activity in isolated guinea pig papillary muscles [EC₂₅ values, concn. required to increase effective refractory period (ERP) 25% above baseline]. Dofetilide, E-4031, sematilide, and d-sotalol, which have been characterized previously as selective IKr blockers, displayed good agreement between K_i values for displacement of 3H-dofetilide binding (47 nM, 38 nM, 12 .mu.M, and .apprx.100 .mu.M, resp.) and EC₂₅ values for increasing ERP in papillary muscles (45.0 nM, 76.9 nM, 20.2 .mu.M and 63.5 .mu.M, resp.). Ibutilide and RP58866, which have been reported to act via mechanisms other than IKr block, had K_i values for displacement of 3H-dofetilide binding (16 nM and 17 nM, resp.) that were .apprx.10-fold lower than EC₂₅ values for increasing ERP in papillary muscles (185.8 nM and 223.5 nM, resp.). The potent displacement of high-affinity 3H-dofetilide binding by ibutilide and RP58866 strongly suggest a role for interaction with IKr in their actions. The discrepant functional activities of these agents, however, suggest a combination of effects beyond those on IKr and implicate modulation of Na⁺ or other K⁺ current subtypes.

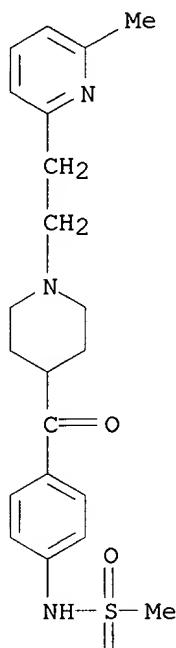
IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(comparison of binding to rapidly activating delayed rectifier K⁺ channel and effects on myocardial refractoriness for class III antiarrhythmic agents)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 113 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:295000 HCAPLUS
DOCUMENT NUMBER: 122:71160
TITLE: Electrophysiological effects of E-4031, a novel class III antiarrhythmic agent
AUTHOR(S): Fujiki, Akira
CORPORATE SOURCE: 2nd Department Internal Medicine, Toyama Medical and Pharmaceutical University, Tomaya, Japan
SOURCE: Cardiovascular Drug Reviews (1994), 12(2), 165-72
CODEN: CDREEA; ISSN: 0897-5957
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 26 refs. Electrophysiol. effects of E-4031, a novel class

Searched by Thom Larson, STIC, 308-7309

III antiarrhythmic agent in humans and lab. animals are discussed.

IT 113559-13-0, E-4031

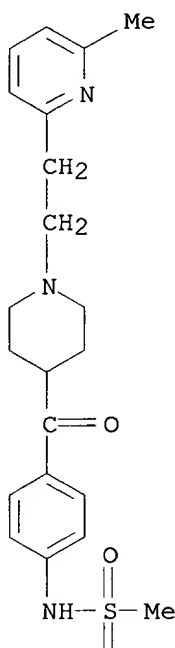
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(electrophysiol. effects of antiarrhythmic E-4031)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 114 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:72384 HCAPLUS
DOCUMENT NUMBER: 122:611
TITLE: Acute cardiovascular and toxic effects of potassium channel blockers in anesthetized primates
AUTHOR(S): Haye, E.; Beatch, G. N.; Adaikan, P. G.; Ratnam, S. S.; Walker, M. J. A.
CORPORATE SOURCE: Department Pharmacology & Therapeutics, University British Columbia, Vancouver, BC, V6T 1Z3, Can.

Searched by Thom Larson, STIC, 308-7309

SOURCE: Proc. West. Pharmacol. Soc. (1994), 37, 5-8
CODEN: PWPSA8; ISSN: 0083-8969

DOCUMENT TYPE: Journal

LANGUAGE: English

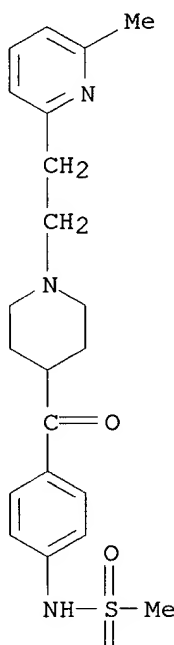
AB In pigtail monkeys and baboons, the Class III antiarrhythmic K⁺ channel blockers ibutilide, E4031, sematilide, and LY190147 prolonged the Q-T interval of the ECG without having major adverse effects on blood pressure and heart rate; the former 2 compds. were more potent than the latter 2 in this respect. The fact that sematilide and LY190147 increased the P-R and QRS intervals, whereas ibutilide and E4031 had lesser effects, suggested that the compds. may act on other cardiac ion channels at the high doses tested. In keeping with its mixed channel actions, tedisamil widened the Q-Tc interval and produced bradycardia, as has been reported in other species. At sufficiently high doses, all the compds., except LY190147, induced arrhythmias in these species, whose cardiac electrophysiol. is presumed to be similar to that of man.

IT **113559-13-0**, E 4031
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(heart electrophysiol. response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



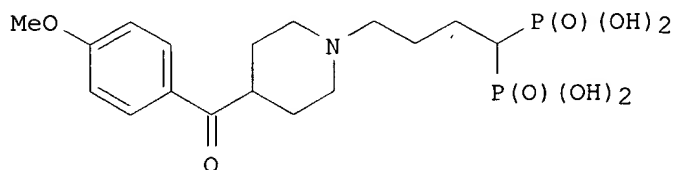
PAGE 2-A

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●2 HCl

L14 ANSWER 115 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:701075 HCAPLUS
 DOCUMENT NUMBER: 121:301075
 TITLE: Preparation of phosphonic acid derivatives useful for
 medically treating hyperlipemia
 INVENTOR(S): Yoshida, Ichirou; Ikuta, Hironori; Fukuda, Yoshio;
 Eguchi, Yoshihito; Kaino, Makoto; Tagami, Katsuya;
 Kobayashi, Naoki; Hayashi, Kenji; Hiyoshi, Hironobu;
 et al.
 PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 363 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|----------|
| WO 9420508 | A1 | 19940915 | WO 1994-JP354 | 19940304 |
| W: AU, CA, CN, FI, HU, JP, KR, NO, NZ, RU, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9461564 | A1 | 19940926 | AU 1994-61564 | 19940304 |
| EP 688325 | A1 | 19951227 | EP 1994-908498 | 19940304 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| HU 72307 | A2 | 19960429 | HU 1995-1944 | 19940304 |
| JP 08508245 | T2 | 19960903 | JP 1994-519819 | 19940304 |
| ZA 9401575 | A | 19941013 | ZA 1994-1575 | 19940307 |
| US 5719303 | A | 19980217 | US 1995-530311 | 19950906 |
| PRIORITY APPLN. INFO.: | | | JP 1993-46389 | 19930308 |
| | | | WO 1994-JP354 | 19940304 |
| OTHER SOURCE(S): | | | MARPAT 121:301075 | |
| GI | | | | |



AB 533 Phosphonic acid derivs. RACRBR1P(O)(OR2)(OR3), e.g., I, or their pharmacol. acceptable salts, useful for medically treating hyperlipemia, were prep'd. The compds. of the present invention act as effective

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squalene synthetase inhibitors (test data given).

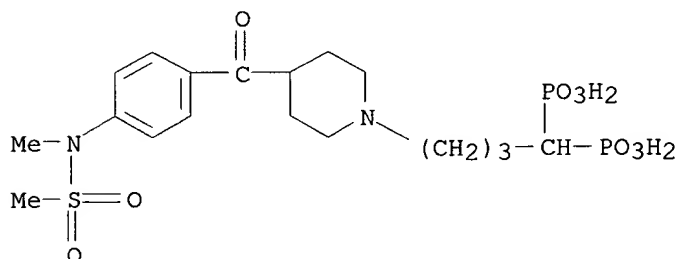
IT 159273-35-5P 159273-36-6P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of phosphonic acid derivs. useful for medically treating hyperlipemia)

RN 159273-35-5 HCAPLUS

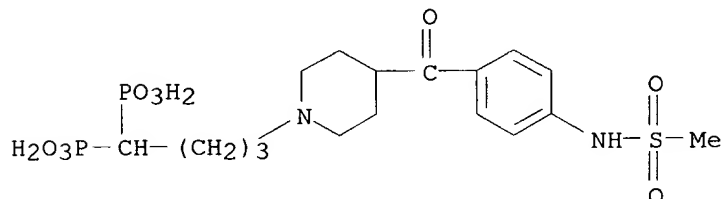
CN Phosphonic acid, [4-[4-[4-[methyl(methylsulfonyl)amino]benzoyl]-1-piperidinyl]butylidene]bis-, tetrasodium salt (9CI) (CA INDEX NAME)



● 4 Na

RN 159273-36-6 HCAPLUS

CN Phosphonic acid, [4-[4-[4-[(methylsulfonyl)amino]benzoyl]-1-piperidinyl]butylidene]bis-, tetrasodium salt (9CI) (CA INDEX NAME)



● 4 Na

L14 ANSWER 116 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:621525 HCAPLUS

DOCUMENT NUMBER: 121:221525

TITLE: Effects of E-4031 on atrial fibrillation threshold in guinea pig atria: comparative study with class I antiarrhythmic drugs

AUTHOR(S): Inoue, Miho; Inoue, Daisuke; Ishibashi, Kazuya; Sakai, Ryuta; Shirayama, Takeshi; Asayama, Jun; Nakagawa, Masao

CORPORATE SOURCE: Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

SOURCE: J. Cardiovasc. Pharmacol. (1994), 24(4), 534-41

CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of E-4031, a new class III antiarrhythmic agent, on atrial fibrillation threshold (AFT), atrial effective refractory period (ERP), and interatrial conduction time (ACT) were investigated in Langendorff-perfused guinea pig hearts; the results were then compared with those of the class I agents disopyramide, procainamide, lidocaine, and flecainide. Whole guinea pig hearts were perfused with Tyrode's soln. contg. acetylcholine (ACh 3×10^{-7} M). The three indexes were measured before and after administration of the test drugs, using right atrial extrastimulus and 50-Hz continuous stimulation. Disopyramide, procainamide, and flecainide (10^{-6} M) significantly increased AFT. Although E-4031 (3×10^{-6} M) also increased AFT, this effect was less potent than that obsd. with the other drugs. E-4031 (10^{-6} M) significantly prolonged ERP, and this prolongation was less pronounced than that obsd. with disopyramide but similar to that obsd. with procainamide or flecainide. E-4031 did not affect ACT, and the greatest prolongation of ACT was obsd. with flecainide. Lidocaine had no effect on any of the indexes. These findings suggest that in guinea pig hearts E-4031 exerts an antifibrillatory effect by prolonging atrial ERP alone, but this effect is less pronounced than that obsd. with class I drugs, because AFT measured by 50-Hz continuous stimulation is influenced by both ERP and ACT.

IT 113559-13-0, E-4031

RL: BAC (Biological activity or effector, except adverse); THU

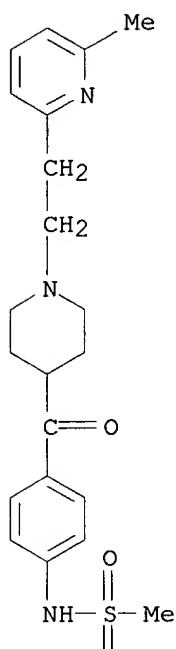
(Therapeutic use); BIOL (Biological study); USES (Uses)

(effect of E-4031 on atrial fibrillation threshold in guinea pig atria and comparison with class I antiarrhythmic drugs)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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PAGE 2-A



● 2 HCl

L14 ANSWER 117 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:570191 HCAPLUS
DOCUMENT NUMBER: 121:170191
TITLE: Effects of E-4031, almokalant and tedisamil on
postrest action potential duration of human papillary
muscles
AUTHOR(S): Ohler, Andreas; Ravens, Ursula
CORPORATE SOURCE: Institute Pharmacokologie, Univ. Gesamthochschule
Essen, Essen, D-45122, Germany
SOURCE: J. Pharmacol. Exp. Ther. (1994), 270(2), 460-5
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The new antiarrhythmic compds. E-4031 {1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methylsulfonyl-aminobenzoyl)piperidine}, almokalant and tedisamil prolonged the action potential duration (APD) of human right ventricular papillary muscle. In order to investigate whether drug-channel interaction takes place during rest, regular stimulation (0.5 Hz) was

interrupted by three 30-min periods of quiescence. Drug was added at the beginning of the second period of rest, the third period was interposed at equil. of drug action. Under predrug control conditions, the first action potential after rest was longer than with regular stimulation, steady state was reached again with a monotonic time course. With E-4031 the first action potential after 30 min of drug exposure during quiescence was similar to predrug control, but drug-induced prolongation of APD developed during further stimulation, indicating drug interaction with open channels. After a third period of quiescence, the first APD remained significantly increased compared to predrug values suggesting that E-4031 may be trapped within the resting channel. With almokalant, however, the first APD after wash-in was already prolonged and APD increased further with regular pacing. The effect was partially reversed during the third period of rest. These findings are compatible with open-channel block or no evidence for trapping. On the other hand, tedisamil prolonged APD but did not change the monophasic time course neither when added during quiescence nor at equil. of drug action. It is concluded that changes in APD after quiescence indicate differences among these drugs in their interactions with channel subtypes controlling repolarization.

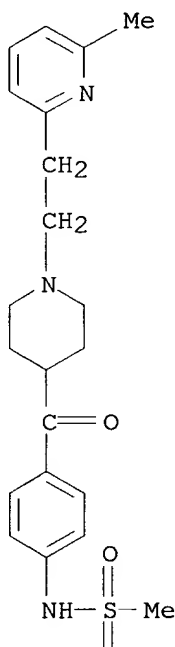
IT **113559-13-0**, E-4031

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Effects of E-4031, almokalant, and tedisamil on postrest action potential duration in human papillary muscle)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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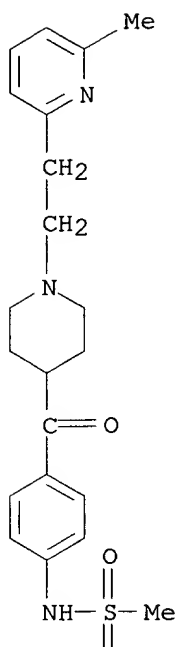
L14 ANSWER 118 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:569799 HCAPLUS
DOCUMENT NUMBER: 121:169799
TITLE: Effects of E-4031 and lidocaine on hemodynamics in rats
AUTHOR(S): Du, Zhimin; Yang, Baofeng
CORPORATE SOURCE: Clinical and Pharmaceutical Inst., Harbin Medical Univ., Harbin, 150086, Peop. Rep. China
SOURCE: Zhongguo Yaoxue Zazhi (1994), 29(5), 276-8
CODEN: ZYZAEU; ISSN: 1001-2494
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The study of the effects of E-4031 and lidocaine on hemodynamics in rats showed that E-4031 and lidocaine given together could decrease blood pressure (Bp) significantly in rats: blood pressure of the control from 12.83 \pm 0.90 to 11.57 \pm 0.81 kPa ($P < 0.01$) and low left ventricular pressure (LVP) from 11.56 \pm 0.76 to 9.47 \pm 0.77 kPa ($P < 0.01$), and could inhibit $+dp/dt_{max}$ from 2531.3 \pm 175.8 to 2014.0 \pm 169.7 mV/s ($P < 0.01$) and $-dp/dt_{max}$ from 2346.0 \pm 175.3 to 1978.0 \pm 159.4 mV/s ($P < 0.05$). Bp, LVP and $\pm dp/dt_{max}$ were decreased after combined use of E-4031 and lidocaine. In the same doses, however, both E-4031 and lidocaine did not affect above parameters. These indicated that the state of cardiac function should be considered carefully when E-4031 and lidocaine were administered jointly to the patient with arrhythmia, and heart failure may be induced if the dose of both drugs is large.

IT **113559-13-0**, E-4031
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(harmful effects of E-4031 combined with lidocaine on hemodynamics in rats)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 119 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:548695 HCAPLUS
 DOCUMENT NUMBER: 121:148695
 TITLE: Comparative effects of increased extracellular potassium and pacing frequency on the class III activities of methanesulfonanilide IKr blockers dofetilide, D-Sotalol, E-4031, and MK-499
 AUTHOR(S): Baskin, Elizabeth P.; Lynch, Joseph J., Jr.
 CORPORATE SOURCE: Dep. Pharmacol., Merck Res. Lab., West Point, PA, USA
 SOURCE: J. Cardiovasc. Pharmacol. (1994), 24(2), 199-208
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The methanesulfonanilide-contg. Class III agents dofetilide, D-sotalol, E-4031, and MK-499 have been characterized as selective blockers of a rapidly activating component of the cardiac delayed rectifier (IK) K⁺ current, IKr. In the present studies, the effects of dofetilide (3-30 nM), D-sotalol (10-100 .mu.M), E-4031 (30-300 nM), and MK-499 (30-300 nM)

Searched by Thom Larson, STIC, 308-7309

on myocardial effective refractory period (ERP) were assessed in ferret right ventricular papillary muscles in conditions of altered extracellular K⁺ concn. [K⁺]_e [normal (4 mM) vs. increased (10 mM)] concns., and of altered pacing frequency (1-3 Hz). With 4 mM [K⁺]_e, all four agents elicited significant, concn.-dependent ERP increases in the frequency range of 1-3 Hz, and all four agents displayed reverse frequency-dependent activity. Reverse frequency-dependent profiles also were demonstrable in 10 mM [K⁺]_e at the higher test agent concns.: dofetilide (10 and 30 nM), D-sotalol (100 .mu.M), E-4031 (100 and 300 nM) and MK-499 (100 and 300 nM). All four agents displayed diminished ERP increases in increased vs. normal [K⁺]_e. Among individual test agents, however, there were differences in magnitudes of diminution of ERP increases obsd. in increased [K⁺]_e: the activities of D-sotalol and MK-499 were better maintained in increased [K⁺]_e than were those of dofetilide and E-4031. As a result of this differential sensitivity increased [K⁺]_e, significant ERP increases were not demonstrable for dofetilide and E-4031 in simultaneous conditions of increased [K⁺]_e and rapid pacing, whereas significant activities were maintained with D-sotalol and MK-499 in increased [K⁺]_e throughout the 1-3 Hz range of pacing frequencies. However, the inherent tendency of myocardial refractoriness to increase in increased [K⁺]_e, particularly at faster pacing frequencies, played a dominant role in detg. the relation between increased vs. normal [K⁺]_e post-treatment ERP in all Class III treatment groups. This frequency-dependent increment in refractoriness in increased [K⁺]_e reflected in baseline ERP detd. in 10 vs. 4 mM [K⁺]_e, resp., at frequencies of 1 Hz (163 vs. 157 ms), 2 Hz (146 vs. 134 ms), and 3 Hz (134 vs. 112 ms) tended to offset as well as minimize differences among the IKr blockers in diminution of activity obsd. in increased [K⁺]_e. As a consequence, no fundamental differences among the methanesulfonanilide IKf blockers were apparent with regard to the influence of altered pacing frequency and [K⁺]_e on effects on abs. refractoriness in this exptl. prepn.

IT 113559-13-0, E-4031

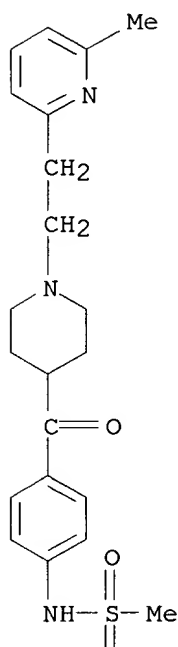
RL: BIOL (Biological study)

(heart pacing frequency and extracellular potassium response to, comparison with other class III antiarrhythmics)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



●2 HCl

L14 ANSWER 120 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:499415 HCAPLUS
DOCUMENT NUMBER: 121:99415
TITLE: Frequency-dependent effects of E-4031, almokalant, dofetilide and tedisamil on action potential duration: no evidence for "reverse use-dependent" block
AUTHOR(S): Ohler, Andreas; Amos, Gregory J.; Wettwer, Erich; Ravens, Ursula
CORPORATE SOURCE: Institut fuer Pharmakologie, Universitaet-Gesamthochschule Essen, Essen, D-45122, Germany
SOURCE: Naunyn-Schmiedeberg's Arch. Pharmacol. (1994), 349(6), 602-10
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antiarrhythmic drugs with class III action are incriminated by "reverse use dependency" which implies preferential block of resting channels. The purpose of the present study was to investigate the frequency dependence

Searched by Thom Larson, STIC, 308-7309

of the effects of 4 new antiarrhythmic compds. on action potential duration (APD) in guinea pig papillary muscle and on delayed rectifier in guinea pig ventricular myocytes in order to scrutinize the concept of reverse use dependency and to obtain evidence for drug-channel interaction. In guinea pig papillary muscles, E-4031, almokalant, dofetilide and tedisamil prolonged APD in a concn.-dependent manner. Drug-induced APD prolongation was not affected by low rates of stimulation (0.2-0.5 Hz). In order to investigate whether drug-channel interaction takes places during rest, regular stimulation (1 Hz) was interrupted by three 30-min periods of quiescence. Drug was added at the beginning of the 2nd period of rest; the 3rd period was interposed at the time of steady state of drug action. With E-4031 and dofetilide no change in shape of the 1st AP after the initial 30 min of drug exposure was obsd. as compared with predrug values, but regular stimulation was required for the full effect to develop. APD did not recover to predrug values after the 3rd period of quiescence. With almokalant and tedisamil, however, the 1st APD after wash-in was already prolonged and the effects increased further with regular pacing. Only with almokalant but not with tedisamil did APD recover during rest. In voltage-clamped guinea pig myocytes, the rapidly activating component of the delayed rectifier was blocked in an analogous manner. It is concluded that the 4 drugs investigated do not bind preferentially to closed channels; instead, open channel block develops with repetitive activation. Therefore, the frequency-dependence of APD prolongation by class III antiarrhythmics must be explained by another mechanism than "reverse use dependency" of block.

IT 113559-13-0, E 4031

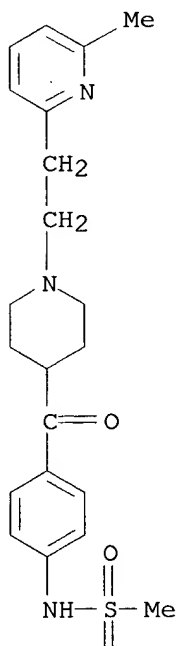
RL: BIOL (Biological study)

(heart action potential duration response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



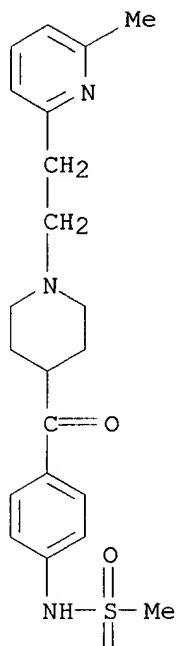
PAGE 2-A

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●2 HCl

L14 ANSWER 121 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:473389 HCAPLUS
DOCUMENT NUMBER: 121:73389
TITLE: Effects of new class-III antiarrhythmic agents, E-4031
and MS-551, on ventricular repolarization in rabbit
hearts
AUTHOR(S): Iwata, Hirokazu; Suzuki, Ryoko; Kodama, Itsuo; Kamiya,
Kaichiro; Toyama, Junji
CORPORATE SOURCE: Res. Inst. Environ. Med., Nagoya Univ., Nagoya,
464-01, Japan
SOURCE: Environ. Med. (1993), 37(1), 79-82
CODEN: ENMEE9; ISSN: 0287-0517
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of E-4031 and MS-551 on ventricular repolarization were
investigated in Langendorff-perfused rabbit hearts. Fifteen to twenty
electrograms were recorded through modified bipolar electrodes from the
anterior epicardial surface of the left ventricle under His-bundle pacing
at 1.0 Hz. In control group hearts, epicardial activation proceeded from
the apex to the base. The interval from the initial sharp neg. deflection
to the apex of the T-wave (Q-aT) in the epicardial electrogram, which
reflects action potential duration at the recording site, was longest at
the apex and shortest at the base. Repolarization, therefore, proceeded
from the base to the apex. Acute application of E-4031 (0.1.mu.M) or
MS-551 (1.mu.M) induced a prolongation of Q-aT in the left ventricle
without affecting the activation sequence. The Q-aT prolongation by
E-4031 was longer in the apex than in the base, giving rise to a
significant enhancement of spatial inhomogeneity of repolarization.
MS-551 caused only a minimal increase in the spatial inhomogeneity of
repolarization. These results could be attributed to the agents'
differing effects on the outward currents responsible for repolarization
of ventricular cells.
IT 113559-13-0, E-4031
RL: BIOL (Biological study)
(heart ventricular repolarization response to MS-551 vs., as
antiarrhythmics)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 122 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:473388 HCAPLUS
 DOCUMENT NUMBER: 121:73388
 TITLE: Comparative investigation of new class-III antiarrhythmic drugs, E-4031 and MS-551, on action potentials and ionic currents in single rabbit ventricular myocytes
 AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Kodama, Itsuo; Toyama, Junji
 CORPORATE SOURCE: Res. Inst. Environ. Med., Nagoya Univ., Nagoya, 464-01, Japan
 SOURCE: Environ. Med. (1993), 37(1), 75-8
 CODEN: ENMEE9; ISSN: 0287-0517
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Effects of new class-III antiarrhythmic agents, E-4031 and MS-551, were investigated on action potential duration (APD) and ionic currents in single rabbit ventricular myocytes. Under 1.0 Hz steady-state

Searched by Thom Larson, STIC, 308-7309

stimulation, both E-4031 (1 .mu.M) and MS-551 (10 .mu.M) prolonged APD. The prolongation of APD by E-4031 (1 .mu.M) was attenuated at higher stimulation frequencies, showing a reversed frequency dependence. Conversely, the prolongation of APD by MS-551 (10 .mu.M) was enhanced at higher rates. In myocytes treated with E-4031 1 .mu.M, the prolongation of APD of a test action potential which was preceded by a train of 1.0 Hz stimulation was maintained at rest durations ranging from 1.0 to 30 s. The APD prolongation by MS-551 (10 .mu.M) however, decreased progressively as the rest duration increased. In voltage clamp expts., both E-4031 (1 .mu.M) and MS-551 (10 .mu.M) induced significant decreases in outward rectifier potassium current (I_K) significantly, but induced no effects on transient outward current (I_{to}). These findings suggest that E-4031 and MS-551 produce differing frequency dependencies in class-III action and that further ionic mechanisms should be clarified.

IT **113559-13-0**, E-4031

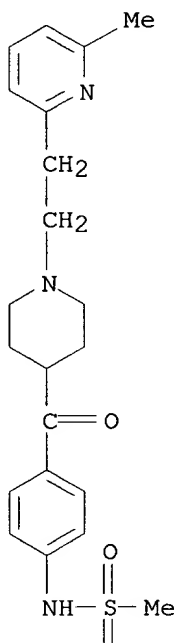
RL: BIOL (Biological study)

(action potential and ionic current response to MS-551 vs., as antiarrhythmic drugs, in ventricular myocytes)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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O

● 2 HCl

L14 ANSWER 123 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:323272 HCAPLUS
 DOCUMENT NUMBER: 120:323272
 TITLE: Preparation of piperidinyll derivatives as
 antithrombotic compounds
 INVENTOR(S): Carr, Albert A.; Dage, Richard C.; Koerner, John E.;
 Li, Tung; Miller, Francis P.; Nieduzak, Thaddeus R.
 PATENT ASSIGNEE(S): Merrell Dow Pharmaceuticals Inc., USA
 SOURCE: U.S., 9 pp. Cont.-in-part of U.S. Ser. No. 673,888,
 abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| US 5292752 | A | 19940308 | US 1992-847971 | 19920305 |
| ZA 9010144 | A | 19911030 | ZA 1990-10144 | 19901217 |
| HU 210590 | B | 19950529 | HU 1990-8370 | 19901220 |
| US 5500433 | A | 19960319 | US 1995-371063 | 19950110 |
| PRIORITY APPLN. INFO.: | | | US 1989-454497 | 19891221 |
| | | | US 1990-604651 | 19901101 |
| | | | US 1991-673888 | 19910322 |
| | | | US 1992-819550 | 19920110 |
| | | | US 1992-930490 | 19920814 |
| | | | US 1993-52848 | 19930426 |
| | | | US 1994-220411 | 19940330 |

OTHER SOURCE(S): MARPAT 120:323272
 GI

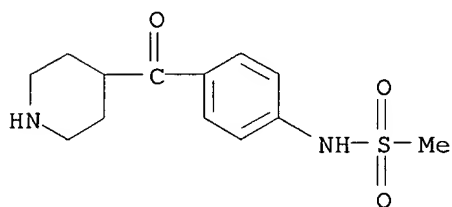


AB Title compds. I (X = CO, SO₂), are prepd. I are also useful as serotonin 5HT₂ antagonists. To N-[4-(4-piperidinylcarbonyl)phenyl]acetamide (prepn. given) in H₂O and THF was added 4-FC₆H₄COCH₂Cl and refluxed to give I (X = O) (II). II prevented thrombi formation at 0.001 mg/kg, i.v., and IC₅₀ 20 nM as serotonin 5HT₂ antagonist.

IT 113559-02-7P 124035-23-0P

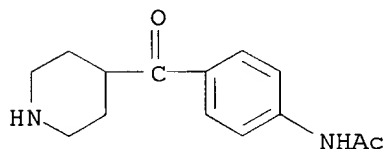
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and reaction of, in prepn. of antithrombotic and serotonin 5HT₂

antagonist)
 RN 113559-02-7 HCAPLUS
 CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-,
 monohydrochloride (9CI) (CA INDEX NAME)

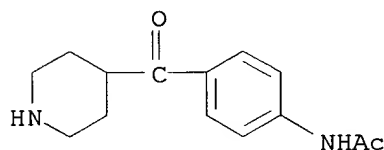


● HCl

RN 124035-23-0 HCAPLUS
 CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]- (9CI) (CA INDEX NAME)



IT **124894-08-2P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
 RN 124894-08-2 HCAPLUS
 CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride (9CI)
 (CA INDEX NAME)



● HCl

L14 ANSWER 124 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:315523 HCAPLUS
 DOCUMENT NUMBER: 120:315523
 TITLE: Shock-induced refractory period extension and
 pharmacologic modulation of defibrillation threshold
 AUTHOR(S): Murakawa, Yuji; Sezaki, Kazunori; Inoue, Hiroshi;
 Usui, Masahiro; Yamashita, Takeshi; Ajiki, Kohsuke;
 Oikawa, Naoki; Iwasawa, Kuniaki; Omata, Masao

Searched by Thom Larson, STIC, 308-7309

CORPORATE SOURCE: 2nd Dep. Intern. Med., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: J. Cardiovasc. Pharmacol. (1994), 23(5), 822-5
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Shock-induced refractory period extension (RPE) has been suggested as a mechanism of elec. defibrillation. The authors measured RPE caused by localized field stimulation measured before and during infusion of disopyramide (n = 5), flecainide (n = 5), or E-4031 (n = 5) in anesthetized dogs and detd. the effect of the drugs in the internal defibrillation threshold (DFT). In the baseline state (n = 15), 16 V/cm S2 field stimulation prolonged the effective RP by 36 \pm 15 ms (22 \pm 12% of RP without S2), whereas 4 and 8 V/cm S2 stimuli did not cause marked RPE. The RPE normalized by the RP without S2 was not significantly influenced by any drug (916 V/cm: disopyramide 30 \pm 11 vs. 27 \pm 11, flecainide 25 \pm 5 vs. 19 \pm 12, and E-4031 18 \pm 13 vs. 22 \pm 14%). Disopyramide did not alter the defibrillation threshold (4.2 \pm 0.6-4.4 \pm 0.6 J). In 2 dogs given flecainide, ventricular fibrillation became refractory to defibrillation. In contrast, E-4031 lowered the threshold from 4.5 \pm 2.4 to 2.2 \pm 1.2 J (p < 0.01). The results suggest that flecainide and E-4031 do not modulate defibrillation efficiency through their effects on RPE.

IT 113559-13-0, E-4031

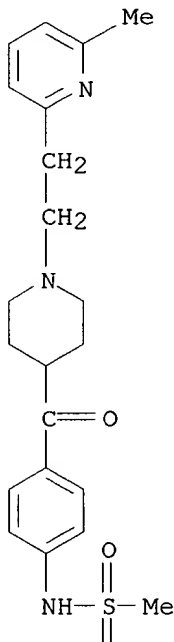
RL: BIOL (Biological study)

(heart refractory period extension in defibrillation shock modulation by)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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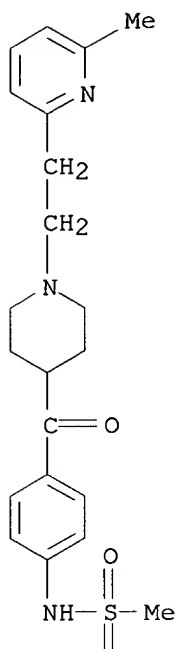
||
O

●2 HCl

L14 ANSWER 125 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:290106 HCAPLUS
DOCUMENT NUMBER: 120:290106
TITLE: Compositions of 3,7-di(cyclopropylmethyl)-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]nonane and 1-[2-(6-methyl-2-pyridyl)ethyl]-4-(methylsulfonylaminobenzoyl)piperidine and use for prevention of ventricular arrhythmias
INVENTOR(S): Bril, Antoine Michel Alain; Gout, Bernard Emile Joseph
PATENT ASSIGNEE(S): Beecham Laboratoires, Fr.
SOURCE: Fr. Demande, 15 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|---|------|----------|-----------------|----------|
| | FR 2690342 | A1 | 19931029 | FR 1992-5217 | 19920428 |
| AB | The title compds. and their pharmaceutically acceptable salts and solvates and derivs. are disclosed for the prevention of ventricular arrhythmia. The dihydrochloride salts of the title compds. were tested in rats with reperfusion-assocd. ventricular arrhythmias. | | | | |
| IT | 113558-89-7 113558-89-7D , derivs. RL: BIOL (Biological study) (di(cyclopropylmethyl) tetramethylenediazabicyclononane and, for ventricular arrhythmia treatment) | | | | |
| RN | 113558-89-7 HCAPLUS | | | | |
| CN | Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME) | | | | |

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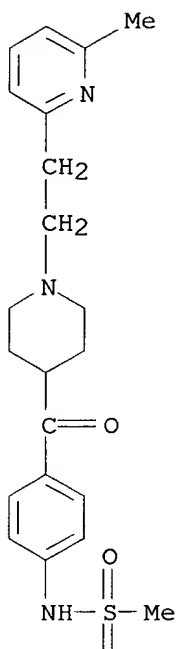


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RN 113558-89-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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IT 113559-13-0

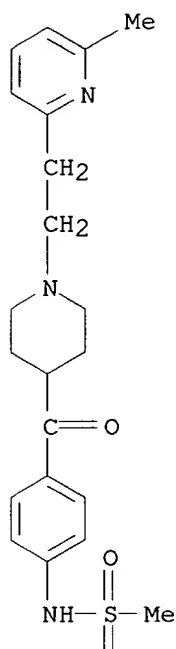
RL: BIOL (Biological study)

(di(cyclopropylmethyl) tetramethylenediazabicyclononane dihydrochloride
and, for ventricular arrhythmia treatment)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 126 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:260927 HCAPLUS
 DOCUMENT NUMBER: 120:260927
 TITLE: Comparison of the cardiac electrophysiologic effects of NE-10064 with sotalol and E-4301 and their modification by simulated ischemia
 AUTHOR(S): McIntosh, M. A.; Tanira, M.; Pacini, D.; Kane, K. A.
 CORPORATE SOURCE: Strathclyde Inst. Drug Res., Univ. Strathclyde, Glasgow, UK
 SOURCE: J. Cardiovasc. Pharmacol. (1994), 23(4), 653-7
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The electrophysiol. effects of a new antiarrhythmic agent NE-10064 were compared with known class III drugs, E-4031 and sotalol, in sheep Purkinje fibers paced at 1 Hz under normal and simulated ischemic conditions. NE-10064 0.3-3 .mu.M and sotalol 0.3-300 .mu.M prolonged action potential duration at 90% of repolarization (APD90) and effective refractory period

Searched by Thom Larson, STIC, 308-7309

(ERP) concn. dependently without affecting APD50 under normal conditions. E-4031 0.3-300 .mu.M prolonged APD50, APD90, and ERP concn. dependently. Percentage increases in APD90 of 20, 27, and 33 were calcd. for NE-10064 3 .mu.M, sotalol 300 .mu.M, and E-4031 1 .mu.M under normal conditions, resp. The concn.-response curves for all three drugs were shifted to the right under simulated ischemic conditions. The shift was more marked for NE-10064 and sotalol. Percentage increases in APD90 of 8, 13, and 23 were obsd. with NE-10064 3 .mu.M, sotalol 300 .mu.M, and E-4031 1 .mu.M during simulated ischemia. NE-10064 exhibits electrophysiol. characteristics similar to those of known class III agents. Its ability to prolong APD90 under normal conditions may explain its antiarrhythmic action in vivo.

IT **113558-89-7**

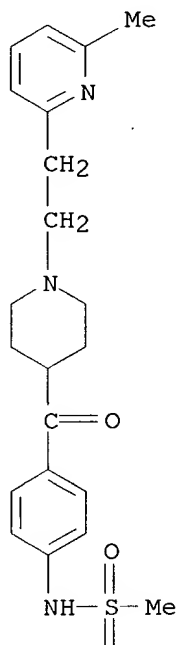
RL: BIOL (Biological study)

(heart electrophysiol. response to, in ischemia, antiarrhythmic activity in relation to)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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L14 ANSWER 127 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:260459 HCAPLUS
 DOCUMENT NUMBER: 120:260459

Searched by Thom Larson, STIC, 308-7309

TITLE: The metabolism and excretion of risperidone after oral administration in rats and dogs

AUTHOR(S): Meuldermans, Willem; Hendrickx, Jan; Mannens, Geert; Lavrijssen, Karel; Janssen, Cor; Bracke, Johan; Le Jeune, Ludo; Lauwers, William; Heykants, Joseph

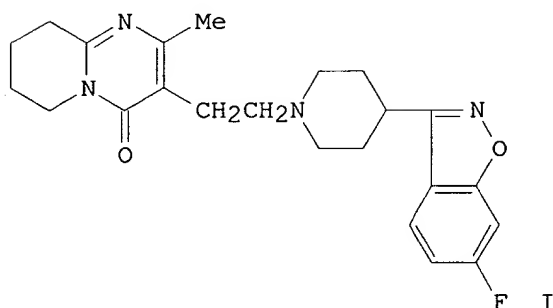
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokin., Janssen Res. Found., Beerse, B-2340, Belg.

SOURCE: Drug Metab. Dispos. (1994), 22(1), 129-38
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



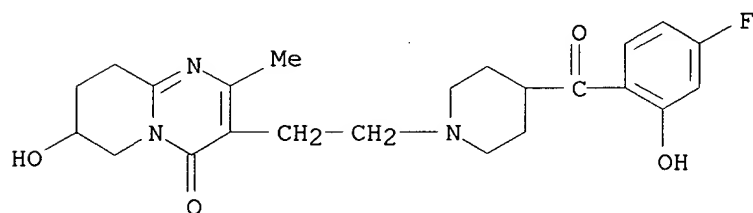
AB The metab. and excretion of risperidone (I), a novel antipsychotic drug, were studied after single p.o. administration of radiolabeled I to rats and dogs. In rats, the excretion of the radioactivity was very rapid. The predominant excretion in rat feces (78-82% of the dose) was related to an extensive biliary excretion of metabolites (72-79% of the dose), only a small part of which underwent enterohepatic circulation. In dogs, about 92% of the dose had been excreted after one week, and the fractions recovered in the urine and feces were comparable. Only a few percent of a p.o. dose was excreted as unchanged I in rats as well as in dogs. Major metabolic pathways of I in rats and dogs were the same as those in humans. The main pathway was the hydroxylation at the alicyclic part of the 6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one moiety. The resulting 9-hydroxy-I (9-OH-I) was the main metabolite in the excreta of dogs. In rats, the metab. was more extensive, resulting in dihydroxy-I and hydroxy-keto-I, which were eliminated mainly via the bile. However, in male and in female dogs, just as in dogs and humans, the active metabolite 9-OH-I was by far the main plasma metabolite. Other major metabolic pathways were the oxidative dealkylation at the piperidine nitrogen and the scission of the isoxazole in the benzisoxazole ring system. The latter pathway appeared to be effected primarily by the intestinal microflora. The mass balance of the metabolites of I in dogs was dose independent from 0.05 to 1.25 mg/kg and was similar to that in humans.

IT 152541-99-6, Metabolite K 152542-00-2, R 72111
152542-00-2D, derivs. 152542-03-5, R 84852
154443-35-3

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, as risperidone metabolite)

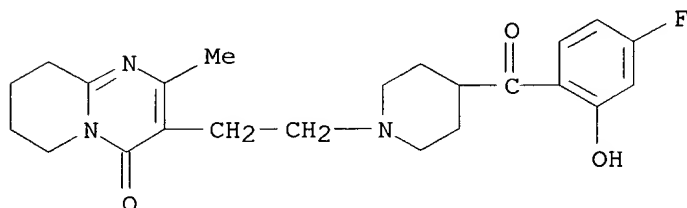
RN 152541-99-6 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



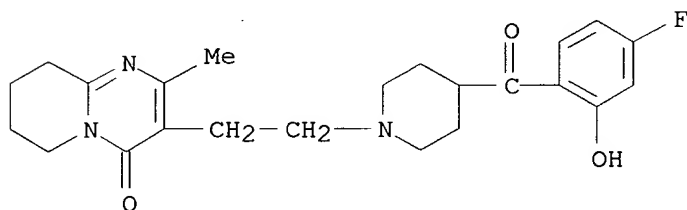
RN 152542-00-2 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



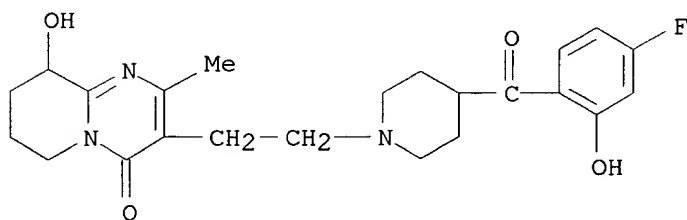
RN 152542-00-2 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)

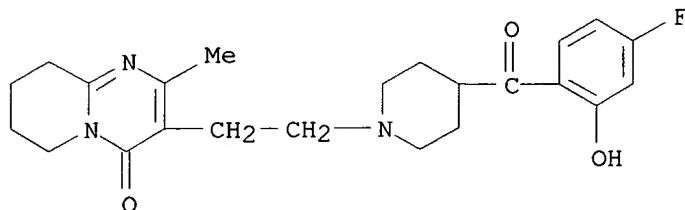


RN 152542-03-5 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

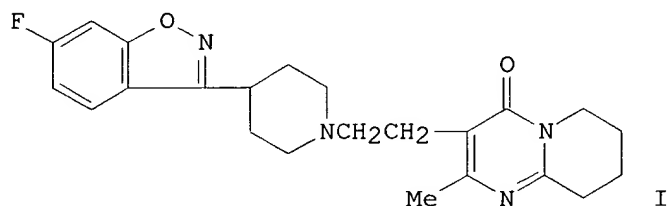


RN 154443-35-3 HCAPLUS
 CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydrodihydroxy-2-methyl- (9CI) (CA INDEX NAME)



2 (D1-OH)

L14 ANSWER 128 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1994:235292 HCAPLUS
 DOCUMENT NUMBER: 120:235292
 TITLE: Absorption, metabolism, and excretion of risperidone in humans
 AUTHOR(S): Mannens, Geert; Huang, May Lynn; Meuldermans, Willem; Hendrickx, Jan; Woestenborghs, Robert; Heykants, Joseph
 CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinet., Janssen Res. Found., Beerse, B-2340, Belg.
 SOURCE: Drug Metab. Dispos. (1993), 21(6), 1134-41
 CODEN: DMDSAI; ISSN: 0090-9556
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The absorption, metab., and excretion of the novel antipsychotic risperidone (I) was studied in three healthy male subjects. One week after a single oral dose of 1 mg [¹⁴C]I 70% of the administered radioactivity was recovered in the urine and 14% in the feces. Unchanged I was mainly excreted in the urine and accounted for 30, 11, and 4% of the administered dose in the poor, intermediate, and extensive metabolizer of debrisoquine, resp. Alicyclic hydroxylation at the 9-position of the tetrahydro-4H-pyrido[1,2-a]-pyrimidin-4-one moiety was the main metabolic pathway. The active metabolite 9-hydroxy-risperidone accounted for 8, 22,

and 32% of the administered dose in the urine of the poor, intermediate, and extensive metabolizer, resp. Oxidative N-dealkylation at the piperidine nitrogen, whether or not in combination with the 9-hydroxylation, accounted for 10-13% of the dose. In methanolic exts. of feces, I and benzisoxazole-opened I and hydroxylated metabolites were detected. 9-Hydroxy-risperidone was by far the main plasma metabolite. The sum of I and 9-hydroxy-risperidone accounted for the largest part of the plasma radioactivity in the three subjects. Although the debrisoquine-type genetic polymorphism plays a distinct role in the metab. of I, the pharmacokinetics of the active fraction (i.e. I plus 9-hydroxy-risperidone) remained similar among the three subjects.

IT 152541-99-6 152542-00-2 152542-03-5

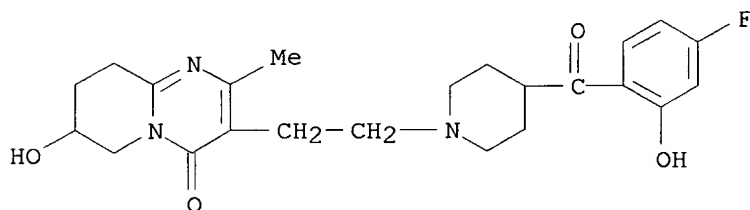
154443-35-3

RL: FORM (Formation, nonpreparative)

(formation of, as risperidone metabolite, in humans)

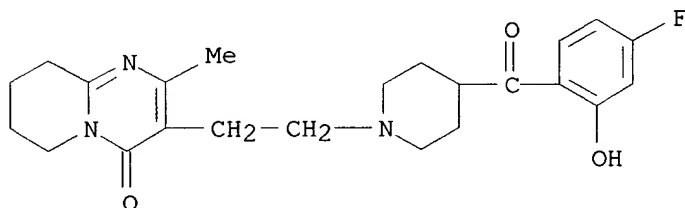
RN 152541-99-6 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-7-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



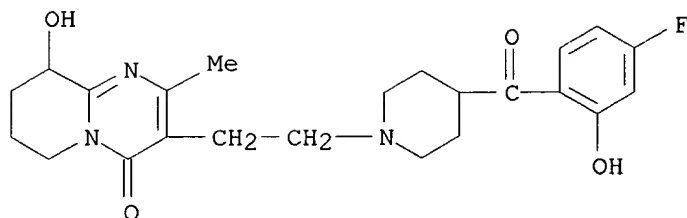
RN 152542-00-2 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl- (9CI) (CA INDEX NAME)



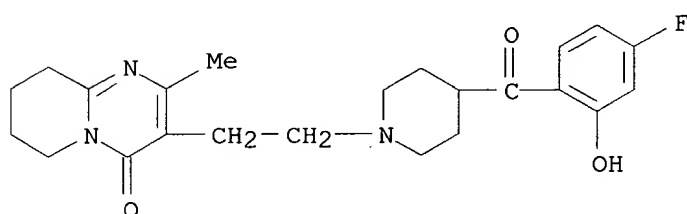
RN 152542-03-5 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 154443-35-3 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydrodihydroxy-2-methyl- (9CI) (CA INDEX NAME)



2 (D1-OH)

L14 ANSWER 129 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:182649 HCAPLUS

DOCUMENT NUMBER: 120:182649

TITLE: Differential class III and glibenclamide effects on action potential duration in guinea pig papillary muscle during normoxia and hypoxia/ischemia

AUTHOR(S): MacKenzie, I.; Saville, V. L.; Waterfall, J. F.

CORPORATE SOURCE: Roche Res. Cent., Welwyn Garden City/Hertfordshire, AL7 3AY, UK

SOURCE: Br. J. Pharmacol. (1993), 110(2), 531-8

CODEN: BJPCBM; ISSN: 0007-1188

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Microelectrode recording techniques were used to study the effects of several potassium channel blockers which are considered to be Class III antiarrhythmic compds. The effects of (+)-sotalol, UK-66,914, UK-68,798 and E-4031 on action potential duration (APD) were detd. in guinea pig isolated papillary muscles. The compds. were evaluated under normoxic or hypoxic/ischemic conditions at 36.5.degree. and compared to glibenclamide, which is considered to be a blocker of ATP-dependent potassium channels. Prolongation of action potential duration at 90% repolarization (APD90) was taken as an indirect measure of potassium channel blockade. Under normoxic conditions, the Class III compds. prolonged APD in a concn.-dependent manner. According to EC15 values, the order of potency of the Class III compds. was found to be UK-68,798 > E-4031 > UK-66,914 > (+)-sotalol. Glibenclamide did not significantly prolong APD90 under

normoxic conditions. Perfusion with an exptl. hypoxic or ischemic bathing soln. produced qual. similar effects on action potentials. Over a period of 20-25 min in either of the exptl. solns., there was a small decrease in action potential amplitude (APA) and a prominent shortening of APD. The ischemic soln. also depolarized the resting membrane potential by about 15 mV. (+)-Sotalol and UK-66,914 did not reverse the shortening of APD induced by perfusion with hypoxic Krebs soln. High concns. of glibenclamide (10 .mu.M) and UK-68,798 (30 and 60 .mu.M) partially reversed the hypoxia-shortened APD. Glibenclamide was more potent and exhibited a greater time-dependent action than UK-68,798. During exptl. ischemia, the Class III compd. E-4031 (10 .mu.M) produced small, but significant, increases in the APD90 (11 ms after 20 min) which were not clearly time-dependent (14 ms after 30 min). UK-68,798 (10 .mu.M) also produced a small, but insignificant, increase in APD90 (12 ms at 20 min). Higher concns. of UK-68,798 (30 and 60 .mu.M) did not produce a consistently significant increase in APD90 during ischemia: significance was only attained after 20 min in the presence of 60 .mu.M UK-68,798 (24 ms). However, in marked contrast to the effects of the Class III compds., glibenclamide (10 .mu.M) produced large time-dependent increases in ischemic APD90 (34 ms at 7 min) which were significant 15 min or more after drug addn. (52 ms at 20 min; 74 ms at 30 min). The present microelectrode data suggest that blockers of ATP-dependent potassium channels, such as glibenclamide, might prove to be more effective than Class III compds. against ischemia-induced shortening of cardiac action potential.

IT **113559-13-0**, E-4031

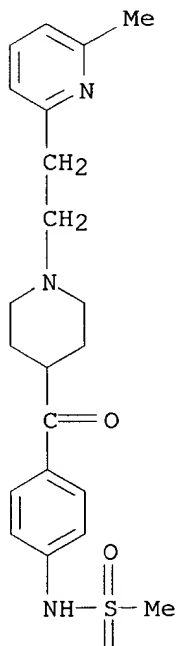
RL: BIOL (Biological study)

(heart action potential response to, in ischemia)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

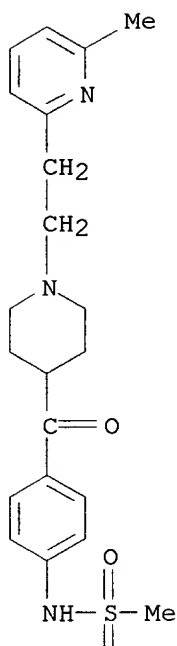
L14 ANSWER 130 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:69199 HCAPLUS
DOCUMENT NUMBER: 120:69199
TITLE: Voltage dependence of cardiac delayed rectifier block
by methanesulfonamide class III antiarrhythmic agents
AUTHOR(S): Krafte, Douglas S.; Volberg, Walter A.
CORPORATE SOURCE: Sterling Winthrop, Collegeville, PA, USA
SOURCE: J. Cardiovasc. Pharmacol. (1994), 23(1), 37-41
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Voltage-clamp expts. were performed on isolated guinea pig ventricular myocytes to examine the voltage dependence of delayed rectifier block by methanesulfonamide-type channel blockers. Voltage-dependent channel block, in which block decreases as membrane potential is made more pos., could contribute to the phenomenon of reverse use dependence, in which the magnitude of the drug-induced prolongation in action potential duration is inversely proportional to stimulation rate. To det. whether such a voltage dependence exists, concn.-response curves were generated for dofetilide, E-4031, sematilide, and DL-sotalol at test potentials ranging 0-60 mV. All these agents blocked current in a manner consistent with selective blockade of the rapidly activating component of delayed rectifier current. The rank order of potency was E-4031 .apprxeq. dofetilide > sematilide > sotalol. Block of tail currents by this class of compds. was more potent after test potentials to +60 mV than after those .ltoreq. 0-10 mV. These data are inconsistent with voltage-dependent channel block being a contributing factor to reverse use-dependence and suggest that other mechanisms must be responsible for this phenomenon.

IT **113559-13-0**, E 4031
RL: BIOL (Biological study)
(heart action potential delayed rectifier block by, voltage dependence of)

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 131 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:69082 HCAPLUS
DOCUMENT NUMBER: 120:69082
TITLE: Effects of Class III antiarrhythmic agents, E-4031 and MS-551 on ventricular repolarization in isolated rabbit hearts
AUTHOR(S): Iwata, Hirokazu; Suzuki, Ryoko; Kamiya, Kaichiro; Kodama, Itsuo; Toyama, Junji
CORPORATE SOURCE: Nagoya, Japan
SOURCE: Kankyo Igaku Kenkyusho Nenpo (Nagoya Daigaku) (1993), 44, 245-7
CODEN: NDKIA2; ISSN: 0369-3570
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Effects of E-4031 (0.1 or 1.0 .mu.M) and MS-551 (10 .mu.M) on ventricular repolarization were studied using changes in surface potentials of isolated rabbit heart as indexes. Results indicated that E-4031 and MS-551 show different effects on the ventricular repolarization.

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E-4031-induced Q-aT-prolonging activity (class III action) was more significant in the apex than in other parts, whereas MS-551-induced Q-aT-prolonging activity was similar in the whole left ventricle area. The E-4031 action indicated an enhanced repolarization inhomogeneity.

IT **113559-13-0**, E-4031

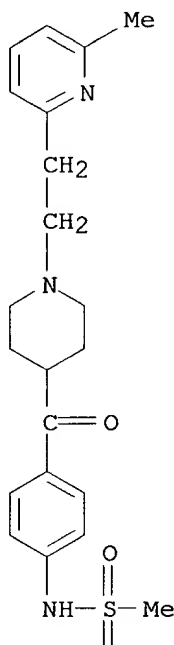
RL: BIOL (Biological study)

(ventricular repolarization response to MS-511 vs., as class III antiarrhythmics)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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L14 ANSWER 132 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:69080 HCAPLUS

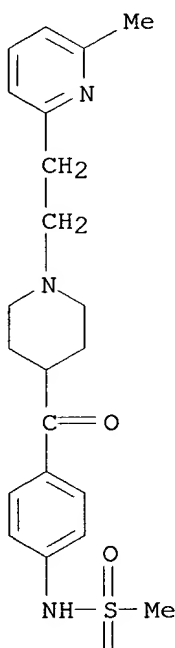
DOCUMENT NUMBER: 120:69080

TITLE: Comparative investigation of new class III antiarrhythmic drugs, E-4031 and MS-551, on electrophysiological properties in isolated rabbit

Searched by Thom Larson, STIC, 308-7309

ventricular myocytes
AUTHOR(S): Cheng, Jianhua; Kamiya, Kaichiro; Kodama, Itsuo;
Toyama, Junji
CORPORATE SOURCE: Nagoya, Japan
SOURCE: Kankyo Igaku Kenkyusho Nenpo (Nagoya Daigaku) (1993),
44, 239-41
CODEN: NDKIA2; ISSN: 0369-3570
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Isolated rabbit ventricular myocytes were perfused with E-403 (0.1-100
.mu.M) or MS-551 (1-100 .mu.M) to investigate their effects on the
electrophysiol. properties. E-4031 prolonged the active potential
duration (APD) at a low stimulation frequency, indicating reverse use
dependency. By contrast, MS-551 markedly prolonged the APD value at a
high stimulation frequency, suggesting use dependency. Thus, class III
antiarrhythmics exert different class III actions at a given stimulation
frequency. E-4031 and MS-551 had no effect on Vmax on active potential
amplitude, characteristics of class III antiarrhythmics. The compds. also
had no effect on the transient outward current (Ito).
IT **113559-13-0**
RL: BIOL (Biological study)
(ventricular myocyte response to, as class III antiarrhythmic,
electrophysiol. properties in relation to)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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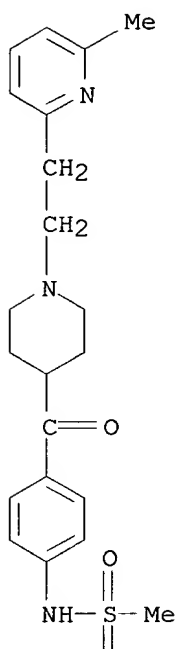
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L14 ANSWER 133 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:69079 HCAPLUS
DOCUMENT NUMBER: 120:69079
TITLE: Electrophysiological effects of MS 551, a new class
III antiarrhythmic agent, on isolated rabbit
ventricular muscles
AUTHOR(S): Suzuki, Ryoko; Kodama, Itsuo; Toyama, Junji
CORPORATE SOURCE: Nagoya, Japan
SOURCE: Kankyo Igaku Kenkyusho Nenpo (Nagoya Daigaku) (1993),
44, 236-8
CODEN: NDKIA2; ISSN: 0369-3570
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Stimulation frequency-dependent APD-prolonging effect (class III action)
of MS-551 was compared with that of E-4031 or sotalol, using isolated
rabbit ventricular muscles. MS-551 at concn. >0.3 .mu.M did not inhibit
the max. upstroke velocity (Vmax) but prolonged the APD with EC50 of 1.9
.mu.M. In contrast to sotalol or E-4031 showing APD-prolonging effect
with reverse use-dependence at 0.1-3.0 Hz, MS-551 showed a mild, biphasic
frequency-dependent APD-prolonging effect with peak value at 0.5 Hz,
indicating that MS-551 inhibits sep. K channel.
IT **113559-13-0**, E-4031
RL: BIOL (Biological study)
(ventricular muscle response to MS-551 vs., as class III
antiarrhythmic, electrophysiol. properties in relation to)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 134 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:641144 HCAPLUS
 DOCUMENT NUMBER: 119:241144
 TITLE: Comparative assessment of ibutilide, D-sotalol, clofilium, E-4031, and UK-68,798 in a rabbit model of proarrhythmia
 AUTHOR(S): Buchanan, Lewis V.; Kabell, Glenn; Brunden, Marshall N.; Gibson, John K.
 CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
 SOURCE: J. Cardiovasc. Pharmacol. (1993), 22(4), 540-9
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Class III agents have been assocd. with development of a polymorphic ventricular tachycardia (PVT) known as torsades de pointes. The authors compared the class III agent ibutilide, which prolongs repolarization through enhancement of an inward sodium current, with the potassium channel blockers E-4031, UK-68,798, clofilium, and D-sotalol for

Searched by Thom Larson, STIC, 308-7309

proarrhythmic effects in an anesthetized rabbit model. In these animals, prolongation of repolarization during .alpha.1 stimulation with methoxamine produces early afterdepolarizations (EADs) and a pause-dependent torsades de pointes-like PVT. Agents were compared over dosage ranges that produced maximal increases in QTc interval and monophasic action potential duration (MAPD). PVT typically developed after atrioventricular (A-V) conduction block and slowing of heart rate (HR), and was preceded by development of repolarization arrhythmias characterized by EADs and triggered activity producing extrasystolic beats. Ibutilide administration resulted in significantly lower EAD amplitudes and a lower incidence of repolarization arrhythmias and PVT as compared with administration of other class III agents. The percentage of rabbits developing PVT for each agent was ibutilide 12%, D-sotalol 70%, E-4031 56%, UK-68,798 69%, and clofilium 80%. Rabbits receiving saline vehicle instead of a class III agent never developed conduction or repolarization abnormalities or PVT. Under the conditions of this study at doses that generate maximal class III effects, ibutilide produces lesser increases in QTc interval and MAPD, and EADs of lower amplitude, resulting in a lower incidence of repolarization arrhythmias and PVT as compared with other class III agents.

IT **113559-13-0**, E-4031

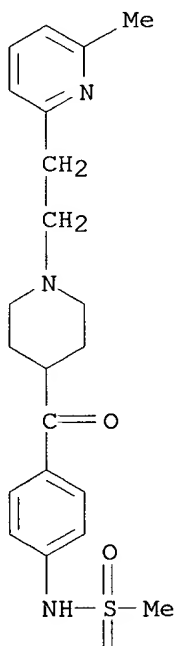
RL: BIOL (Biological study)

(torsades de pointes induction by, as class III antiarrhythmic)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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L14 ANSWER 135 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:641130 HCAPLUS

DOCUMENT NUMBER: 119:241130

TITLE: Comparative efficacy of antiarrhythmic agents in preventing halothane-epinephrine arrhythmias in rats
AUTHOR(S): Takada, Koji; Sumikawa, Koji; Kamibayashi, Takahiko; Hayashi, Yukio; Yamatodani, Atsushi; Kawabata, Kazunaga; Yoshiya, Ikuto

CORPORATE SOURCE: Med. Sch., Osaka Univ., Osaka, 553, Japan

SOURCE: Anesthesiology (1993), 79(3), 563-70

CODEN: ANESAV; ISSN: 0003-3022

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Because the relative efficacy of antiarrhythmic agents on halothane-epinephrine arrhythmias was not well characterized, this study was undertaken to comparatively evaluate the antiarrhythmic action of Na⁺, K⁺ and Ca²⁺-channel blockers on epinephrine-induced ventricular arrhythmias during halothane anesthesia in rats. Rats were anesthetized at random with either halothane (15%), isoflurane (2.0%), or pentobarbital (50 mg/kg i.p.), and the lungs were mech. ventilated with O₂. The rats were studied in 3 consecutive protocols. Protocol I detd. the arrhythmogenic thresholds of epinephrine during the 3 types of anesthesia in 33 rats. Protocol II detd. the arrhythmogenic thresholds of epinephrine during halothane anesthesia in 64 rats receiving saline (control) or one of 5 antiarrhythmic agents. Protocol III measured the duration of epinephrine-induced arrhythmias during halothane anesthesia in 42 rats receiving saline (control) or one of 5 antiarrhythmic agents. In protocol I, the arrhythmogenic doses of epinephrine during halothane, isoflurane, or pentobarbital anesthesia were 1.7 , 11.1 , and 39.0 .mu.g/kg, resp., and the corresponding plasma concns. were 4.3 , 103.7 , and 246.7 ng/mL, resp. In protocol II, the arrhythmogenic doses were similar in rats receiving saline and in those receiving lidocaine. The arrhythmogenic doses in rats receiving verapamil, flecainide (Na⁺ and K⁺-channel blocker), E-4031 (K⁺-channel blocker), or amiodarone (K⁺-channel blocker with Na⁺-, Ca²⁺-, and beta-blocking activity) increased , i.e., 4.2, 5.5, and 31.7 times control (P <0.01). In protocol III, lidocaine had no effect on the duration of arrhythmias. Flecainide, E-4031, and verapamil markedly reduced the duration of arrhythmias induced by epinephrine, 8 .mu.g/kg i.v. (P <0.01), whereas only amiodarone markedly reduced the duration of arrhythmias induced by epinephrine, 16 .mu.g/kg i.v. (P <0.01). It was concluded that agents with K⁺-channel blocking properties were the most effective in preventing halothane-epinephrine arrhythmias in rats.

IT 113559-13-0, E-4031

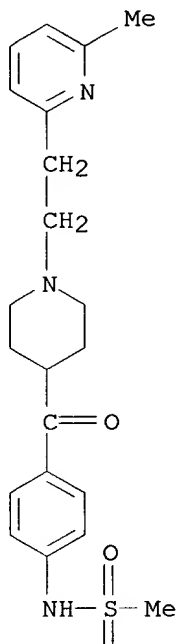
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)

(antiarrhythmic activity of, in halothane anesthesia-epinephrine

arrhythmias)
 RN 113559-13-0 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 136 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:641096 HCAPLUS
 DOCUMENT NUMBER: 119:241096
 TITLE: Effects of antiarrhythmic agents on low-perfusion induced arrhythmia in isolated rat heart
 AUTHOR(S): Ohta, Hideo
 CORPORATE SOURCE: Sch. Med., Niigata Univ., Niigata, 951, Japan
 SOURCE: Niigata Igakkai Zasshi (1993), 107(6), 512-22
 CODEN: NIGZAY; ISSN: 0029-0440
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 AB In the isolated perfused rat heart, low-flow perfusion (0.5 mL/min) resulted in a marked redn. of the left ventricular developed pressure.

Searched by Thom Larson, STIC, 308-7309

Ventricular arrhythmia developed and the ventricular end-diastolic pressure rose 10 min after initiation of low-flow perfusion. In the vehicle treated hearts the total arrhythmic period during 20 min of low-flow perfusion was 436 \pm 36 s. The period was shorter in the presence of lidocaine, diltiazem and propranolol and the rise of EDP was attenuated. E-4031, a blocker of the delayed rectifier K channel, produced a shortening of the arrhythmic period and an attenuation of the rise of EDP only at a high concn. (100 μ M). In contrast, glibenclamide, a blocker of ATP-sensitive K channel, and bretylium, a quaternary ammonium salt, reduced arrhythmic period without producing attenuation of the rise of EDP. These effects were inhibited by cromakalim, an ATP-sensitive K channel opener. Thus, the antiarrhythmic effects of diltiazem, propranolol, lidocaine and E-4031 were due to antiischemic action, while those of glibenclamide and bretylium were probably attributable to blockade of ATP-sensitive K channel.

IT 113559-13-0, E-4031

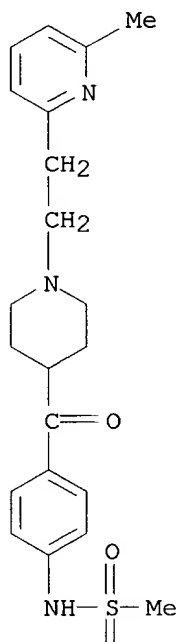
RL: BIOL (Biological study)

(arrhythmia treatment by, cromakalim and potassium channel in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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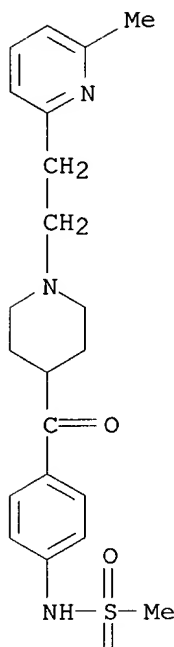
PAGE 2-A

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L14 ANSWER 137 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:595350 HCAPLUS
DOCUMENT NUMBER: 119:195350
TITLE: Electrophysiological and inotropic effects of H 234/09
(almokalant) in vitro: A comparison with two other
novel IK blocking drugs, UK-68798 (dofetilide) and
E-4031
AUTHOR(S): Abrahamsson, C.; Duker, G.; Lundberg, C.; Carlsson, L.
CORPORATE SOURCE: Preclin. Res. Dev., Astra Haessle, Moelndal, S-431 83,
Swed.
SOURCE: Cardiovasc. Res. (1993), 27(5), 861-7
CODEN: CVREAU; ISSN: 0008-6363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to compare the electrophysiol. and inotropic
effects of the novel class III agents H 234/09, UK-68798, and E-4031 in
vitro. The electrophysiol. effects were investigated by recording
transmembrane action potentials in the isolated ventricular muscle and
Purkinje fibers of the rabbit; effects on force (adjusted to the max.
isoprenaline response) and refractoriness were investigated in the
isolated cat papillary muscle. It was shown that all the drugs induced a
concn. dependent prolongation of the action potential duration, which was
much more pronounced in the Purkinje fibers than in the ventricular
muscle. However, when compared at concns. giving a 15% increase of the
action potential duration in ventricular muscle, H 234/09 was
significantly less effective in the Purkinje fibers than the other two
drugs. In the cat papillary muscle all drugs induced an increase in force
development. This increase tended to parallel the increase in effective
refractory period. However, at prolongations of effective refractory
period of more than approx. 50% the increase in developed force levelled
off. All the class III agents investigated showed a pos. inotropic
effect, which may be of advantage when compared to conventional class I
antiarrhythmic agents, which have cardiodepressant actions. Compared to
UK-68798 and E-4031, H 234/09 showed a less unfavorable profile in terms
of dispersion of repolarization, which theor. may reduce the risk of
arrhythmias assocd. with delayed repolarization. However, this less
unfavorable profile must, like the pos. inotropic effect, ultimately be
investigated in clin. trials.
IT **113559-13-0**, E-4031
RL: BIOL (Biological study)
(heart electrophysiol. and inotropic response to, as class III
antiarrhythmic and potassium channel blocker)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 138 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:552629 HCAPLUS
DOCUMENT NUMBER: 119:152629
TITLE: Anion and cation modulation of the guinea pig
ventricular action potential during
.beta.-adrenoceptor stimulation
AUTHOR(S): Levesque, P. C.; Clark, C. D.; Zakarov, S. I.;
Rosenshtraukh, L. V.; Hume, J. R.
CORPORATE SOURCE: Sch. Med., Univ. Nevada, Reno, NV, 89557-0046, USA
SOURCE: Pfluegers Arch. (1993), 424(1), 54-62
CODEN: PFLABK; ISSN: 0031-6768
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Modulation of the ventricular action potential by .beta.-adrenergic
activation of Ca²⁺, K⁺ and cAMP-dependent Cl⁻ channels was assessed in
enzymically isolated guinea pig ventricular myocytes. The effectiveness
and relative selectivity of 9-anthracene carboxylic acid (9-AC) as an
antagonist of cAMP-dependent Cl⁻ channels was also tested. Membrane
currents and action potentials were recorded using the conventional

Searched by Thom Larson, STIC, 308-7309

whole-cell variant of the patch-clamp technique or with the amphotericin B perforated-patch technique. The .beta.-adrenergic agonist isoproterenol either increased or decreased action potential duration depending on whether the dominant effect was on inward Ca²⁺ currents or on outward K⁺ or Cl⁻ currents. When Ca²⁺ and K⁺ channel modulations were prevented by nisoldipine and low temp., resp., .beta.-adrenergic activation of Cl⁻ channels caused a significant redn. in action potential duration and a slight depolarization of the membrane potential. The .beta.-adrenergic-mediated effects were reversed by the Cl⁻ channel blocker, 9-AC. In the absence of .beta.-adrenergic stimulation, 9-AC had no detectable effects on action potentials or Ca²⁺ currents. Apparently, .beta.-adrenergic activation of Cl⁻ channels is a potent mechanism for regulation of action potential duration, and 9-AC may be a useful, relatively specific, pharmacol. tool for evaluating the physiol. role of cAMP-activated Cl⁻ channels in heart. 9-AC also reversed the ability of isoproterenol to antagonize prolongation of action potential duration by the class III antiarrhythmic agent E 4031.

IT 113559-13-0, E 4031

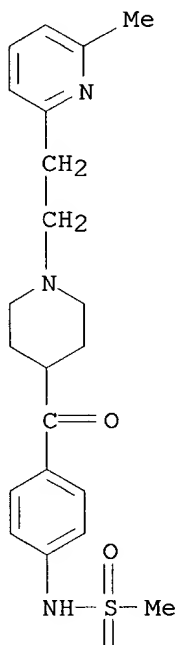
RL: BIOL (Biological study)

(heart action potential modulation by, during .beta.-adrenoceptor stimulation)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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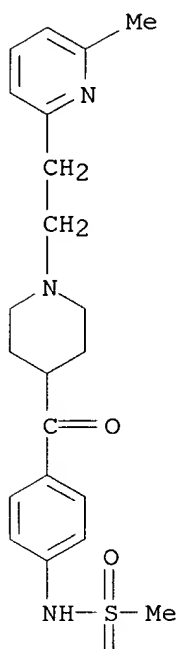
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L14 ANSWER 139 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:531254 HCAPLUS
DOCUMENT NUMBER: 119:131254
TITLE: Antiarrhythmic drugs, clofilium and cibenzoline are
potent inhibitors of glibenclamide-sensitive potassium
currents in *Xenopus* oocytes
AUTHOR(S): Sakuta, Hidenari; Okamoto, Koichi; Watanabe, Yasuhiro
CORPORATE SOURCE: Dep. Pharmacol., Natl. Defense Med. Coll., Tokorozawa,
359, Japan
SOURCE: Br. J. Pharmacol. (1993), 109(2), 866-72
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel K⁺ channel opener, Y-26763 induced outward K⁺ currents in
voltage-clamped follicle-enclosed *Xenopus* oocytes in a concn.-dependent
manner with an EC₅₀ value of 58 .mu.M. The Y-26763-induced K⁺ current was
completely and reversibly blocked by glibenclamide (an ATP-sensitive K⁺
channel blocker) in a concn.-dependent manner (IC₅₀ 140 nM). Effects of
several antiarrhythmic drugs on Y-26763-induced glibenclamide-sensitive K⁺
currents were investigated. (.+-.)-Cibenzoline, RS-2135, pirlmenol,
lorcainide and KW-3407 (class I antiarrhythmic drugs, Na⁺ channel
blockers) suppressed Y-26763 responses in a concn.-dependent manner with
IC₅₀ values (in .mu.M) of 6.6, 54, 68, 71 and 370, resp. Clofilium,
E-4031, MS-551 and bretylium (class III antiarrhythmic drugs which
increase the action potential duration) also suppressed Y-26763 responses
concn.-dependently, IC₅₀ values (in .mu.M) were 3.3, 660, 980 and
.gtoreq.2000, resp. N-acetylprocainamide (class III antiarrhythmic drug)
scarcely suppressed Y-26763 responses. The glibenclamide-sensitive K⁺
currents elicited by KRN2391 were also suppressed by all these
antiarrhythmic drugs. The antiarrhythmic drugs, clofilium and
(.+-.)-cibenzoline block glibenclamide-sensitive K⁺ channels in *Xenopus*
oocytes at concns. comparable to their therapeutic plasma levels.
IT **113559-13-0**, E-4031
RL: BIOL (Biological study)
(potassium channel response to, as antiarrhythmic agent)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 140 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:531211 HCAPLUS
 DOCUMENT NUMBER: 119:131211
 TITLE: Suppressive effects of nicorandil on early afterdepolarization induced by class III antiarrhythmic drug
 AUTHOR(S): Kasama, Masafumi; Tsutsumi, Takeshi; Miyamoto, Norio; Mashima, Saburo
 CORPORATE SOURCE: Fijigaoka Hosp., Showa Univ., Yokohama, Japan
 SOURCE: Ther. Res. (1993), 14(3), 825-9
 CODEN: THREEL; ISSN: 0289-8020
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 AB Nicorandil prevented the appearance of early afterdepolarization induced in canine Purkinje fibers by the Class III antiarrhythmic drug E-4031. Nicorandil may be useful in suppressing the proarrhythmia induced by Class III antiarrhythmics.
 IT 113559-13-0, E-4031

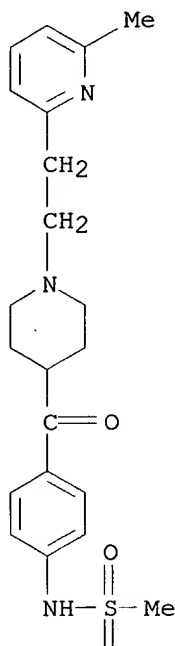
RL: BIOL (Biological study)

(heart Purkinje fiber early afterdepolarization from, nicorandil suppression of)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● 2 HCl

L14 ANSWER 141 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:440949 HCAPLUS

DOCUMENT NUMBER: 119:40949

TITLE: Preparation of piperidinyl and piperazinyl derivatives as antiarrhythmics

INVENTOR(S): Butera, John A.; Bagli, Jehan F.; Ellingboe, John W.

PATENT ASSIGNEE(S): American Home Products Corp., USA

SOURCE: U.S., 9 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

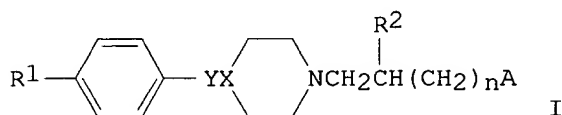
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|------------------|----------|
| US 5202346 | A | 19930413 | US 1992-841922 | 19920225 |
| US 5254689 | A | 19931019 | US 1992-957568 | 19921007 |
| PRIORITY APPLN. INFO.: | | | US 1992-841922 | 19920225 |
| OTHER SOURCE(S): | | | MARPAT 119:40949 | |
| GI | | | | |



AB The title compds. I [R1 = alkylsulfonamido, arylsulfonamido, NO2, CN, imidazol-1-yl, 1,2,4-triazol-1-yl; Y = CO, CH(OH), CH2, O, S, SO2; X = CH, N; R2 = H, OH; when n = 0, R2 = H; n = 0, 1-6; A = substituted OPh or pyridin-2-yl] are prepd. as class III antiarrhythmics. The condensation of 4-(4-methylsulfonylaminobenzoyl)piperidine-HCl with 1-(4-nitrophenoxy)-2-bromoethane in K2CO3-contg. DMF gave N-[4-[[1-[2-(4-nitrophenoxy)ethyl]-4-piperidinyl]carbonyl]phenyl]methanesulfonamide (II). The i.v. administration of 0.05 mg II/kg caused electrophysiol. change characteristic of class III antiarrhythmic activity in dogs with exptl. arrhythmia.

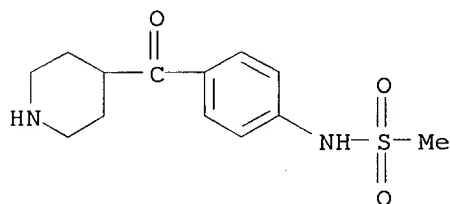
IT **113559-02-7**

RL: RCT (Reactant)

(condensation of, with nitrophenoxybromoethane)

RN 113559-02-7 HCAPLUS

CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



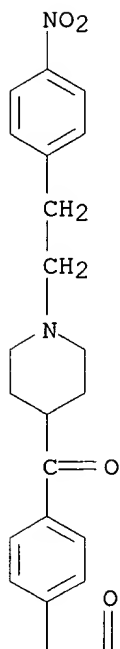
● HCl

IT **148505-35-5P 148505-37-7P 148505-41-3P****148505-42-4P 148505-44-6P**RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiarrhythmic)

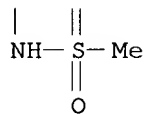
RN 148505-35-5 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-nitrophenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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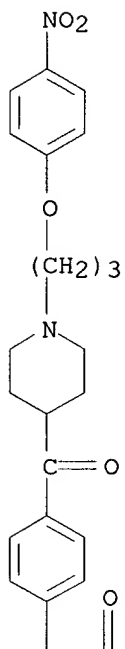


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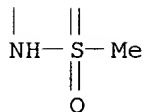


RN 148505-37-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(4-nitrophenoxy)propyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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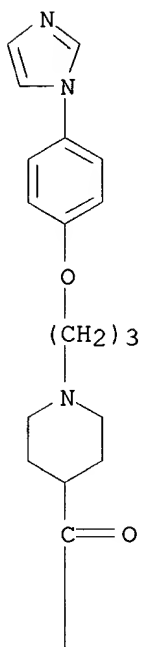


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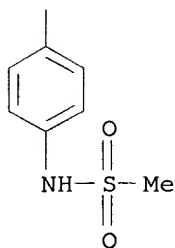


RN 148505-41-3 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[3-[4-(1H-imidazol-1-yl)phenoxy]propyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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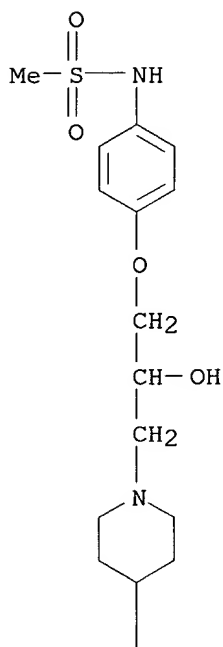


PAGE 2-A

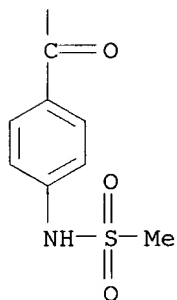


RN 148505-42-4 HCAPLUS
CN Methanesulfonamide, N-[4-[2-hydroxy-3-[4-[4-[(methanesulfonyl)amino]benzoyl]-1-piperidinyl]propoxy]phenyl]- (9CI) (CA INDEX NAME)

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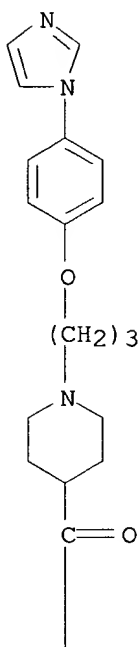


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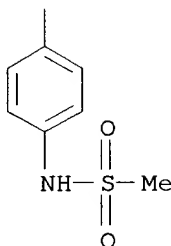


RN 148505-44-6 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[3-[4-(1H-imidazol-1-yl)phenoxy]propyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 142 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:400640 HCAPLUS
DOCUMENT NUMBER: 119:640
TITLE: Absence of effects of class II antiarrhythmic agents
on cloned cardiac potassium channels
AUTHOR(S): Yamagishi, Toshio; Ishii, Kuniaki; Taira, Norio
CORPORATE SOURCE: Sch. Med., Tohoku Univ., Sendai, 980, Japan
SOURCE: Jpn. J. Pharmacol. (1993), 61(4), 371-3
CODEN: JJPAAZ; ISSN: 0021-5198
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Thom Larson, STIC, 308-7309

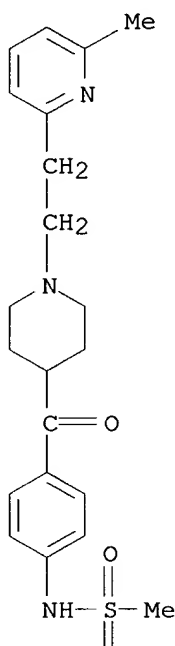
AB The authors investigated the effects of class III antiarrhythmic agents, d-sotalol, E-4031 and MS-551, on the currents of two cloned K channels, Kv1.2 (IKv1.2) and Kv1.4 (IKv1.4), by using the Xenopus oocyte expression system. Both IKv1.2 and IKv1.4 were sensitive to 4-aminopyridine and quinidine, but insensitive to tetraethylammonium, d-sotalol, E-4031 and MS-551. The results suggest that some types of structural proteins may be necessary for class III agents to inhibit the cardiac cloned K channels.

IT **113559-13-0**, E-4031
 RL: BIOL (Biological study)
 (heart potassium channels response to, antiarrhythmic activity in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 143 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:225314 HCAPLUS
 DOCUMENT NUMBER: 118:225314

Searched by Thom Larson, STIC, 308-7309

TITLE: Membrane activity of class III antiarrhythmic compounds; a comparison between ibutilide, d-sotalol, E-4031, sematilide and dofetilide

AUTHOR(S): Lee, Kai S.; Tsai, T. D.; Lee, Esther W.

CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49007, USA

SOURCE: Eur. J. Pharmacol. (1993), 234(1), 43-53
CODEN: EJPHAZ; ISSN: 0014-2999

DOCUMENT TYPE: Journal

LANGUAGE: English

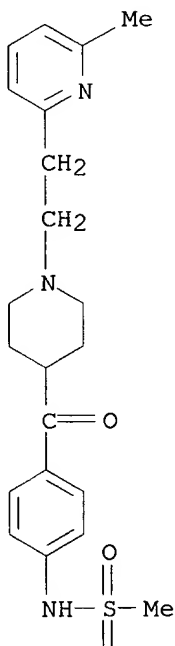
AB The membrane activity of ibutilide, d-sotalol, sematilide, E-4031, and dofetilide was compared on isolated guinea pig heart ventricular cells. Ibutilide and dofetilide produced a bell-shaped concn.-dependent effect on the action potential duration. Ionic current measurements showed that ibutilide at 10^{-8} M increased a late inward current; the other compds. had either no effect or decreased the current. Only ibutilide at 10^{-5} M increased an outward current, as opposed to a uniform depression of the repolarization current I_K by sotalol, sematilide, E-4031, and dofetilide; the depression of I_K by the latter compds. could be reversed by 10^{-5} M ibutilide. Low concns. of ibutilide could further prolong the action potential duration that had already been prolonged by K^+ channel blockers, but high concns. of ibutilide did just the opposite by reversing the prolongation caused by K^+ channel blockers. Thus, the action potentials agree well with the ionic current results. Possible mechanistic advantages of ibutilide over K^+ channel blockers are discussed.

IT **113559-13-0**, E-4031
RL: BIOL (Biological study)
(heart myocyte elec. currents responses to, antiarrhythmic activity in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

L14 ANSWER 144 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:225308 HCAPLUS

DOCUMENT NUMBER: 118:225308

TITLE: Electrophysiologic effects of a new class III antiarrhythmic agent, E-4031, on atrial flutter, atrial refractoriness, and conduction delay in a canine sterile pericarditis model

AUTHOR(S): Shimizu, Akihiko; Kaibara, Muneshige; Centurion, Osmar A.; Kapuku, Gaston; Hirata, Tetsuya; Fukatani, Masahiko; Yano, Katsusuke; Hashiba, Kunitake

CORPORATE SOURCE: Sch. Med., Nagasaki Univ., Nagasaki, 852, Japan

SOURCE: J. Cardiovasc. Pharmacol. (1993), 21(4), 656-62

CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Numerous studies have shown that E-4031 generally prolongs the atrial effective refractory period (AERP) without affecting cardiac conduction. The effects of E-4031 on AERP and cardiac conduction at short cycle lengths (CLs) close to the AERP were measured in 12 dogs with sterile pericarditis. Three pairs of electrodes were sutured at three sites in the atria 4 days after the model was created. We measured AERP and max. conduction delay (MCD) after 8 beats train at CLs of 400, 300, 200 and 150 ms before and during continuous infusion of E-4031 (0.1 .mu.g/kg/min) that followed an initial dose of 10 mg/kg/min/5 min.

IT 113559-13-0, E-4031

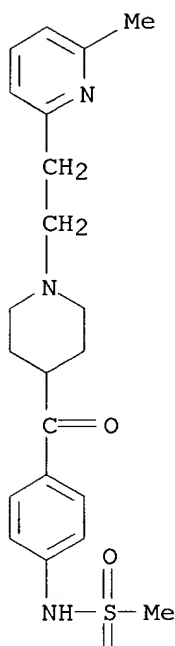
RL: BIOL (Biological study)

(as antiarrhythmic, heart atria electrophysiol. response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

L14 ANSWER 145 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:183121 HCAPLUS
DOCUMENT NUMBER: 118:183121
TITLE: Antifibrillatory effects of class III antiarrhythmic drugs: comparative study with flecainide
AUTHOR(S): Usui, Masahiro; Inoue, Hiroshi; Saihara, Shinichiro; Sugimoto, Tsuneaki
CORPORATE SOURCE: 2nd Dep. Intern. Med., Tokyo Univ. Hosp., Tokyo, 113, Japan
SOURCE: J. Cardiovasc. Pharmacol. (1993), 21(3), 376-83
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antifibrillatory effects of flecainide 1 mg/kg + 0.05 mg/kg/min i.v., bretylium 6 mg/kg i.v., D-sotalol 2 mg/kg + 0.1 mg/kg/min i.v., and E-4031, a new class III drug, 50 .mu.g/kg + 5 .mu.g/kg/min i.v. were compared with three different methods of detg. ventricular fibrillation threshold (VFT) in anesthetized open-chest dogs. In protocol 1, VFT was

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detd. with 2-S, 50-Hz continuous pulses. Flecainide prolonged intraventricular conduction time (CT) and ventricular effective refractory period (ERP) and increased VFT significantly. Bretylium prolonged ERP slightly, but did not increase VFT significantly. Both D-sotalol and E-4031 prolonged ERP and increased VFT. In protocol 2, VFT was detd. with the extrastimulus technique in dogs, with localized ventricular necrosis produced with protease. Flecaïnide, D-sotalol, and E-4031 restored VFT, which had been decreased by protease injection, to the baseline level, whereas bretylium did not. In protocol 3, the train pulse method with 100-Hz train pulses covering the vulnerable period was used in the same dogs used for protocol 2. Flecaïnide, bretylium, and D-sotalol increased VFT, but E-4031 did not. The antifibrillatory effects of class III drugs differ depending on the method of VFT detn. The present data suggest that the antifibrillatory effects of antiarrhythmic drugs should be assessed by different methods of VFT detn.

IT **113559-13-0**, E-4031

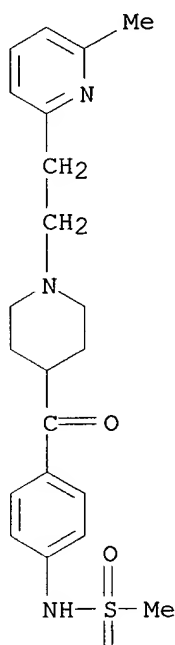
RL: BIOL (Biological study)

(ventricular fibrillation inhibition by)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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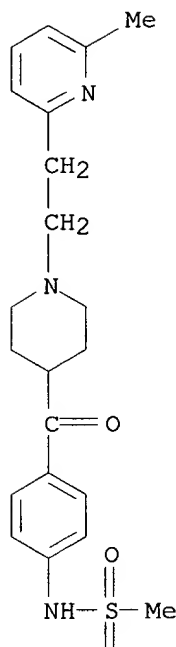
PAGE 2-A

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●2 HCl

L14 ANSWER 146 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:139506 HCAPLUS
DOCUMENT NUMBER: 118:139506
TITLE: The clinical benefits of E-4031, a novel class III antiarrhythmic drug, on myocardial contractility
AUTHOR(S): Nawada, Takahiro; Doi, Tetsuya; Hisatome, Ichiro; Tanaka, Yasunori; Kotake, Hiroshi; Mashiba, Hiroto
CORPORATE SOURCE: Fac. Med., Tottori Univ., Yonago, 683, Japan
SOURCE: Yonago Acta Med. (1992), 35(3), 217-20
CODEN: YOAMAQ; ISSN: 0513-5710
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many antiarrhythmic drugs that belong to classes I and IV of the Vaughan Williams classification have been known to cause myocardial depression. In this study, we obsd. the inotropic effect of E-4031, a novel class III antiarrhythmic drug, compared with that of class I and class IV antiarrhythmic drugs. The study revealed that E-4031 does not have a significant inotropic effect. With clin. efficacy for reentrant tachycardia, E-4031 was considered to be a suitable antiarrhythmic agent for patients with myocardial failure.
IT 113559-13-0, E-4031
RL: BIOL (Biological study)
(antiarrhythmic, heart contraction response to)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 147 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:94087 HCAPLUS
DOCUMENT NUMBER: 118:94087
TITLE: Actions of pinacidil at a reduced potassium concentration: A direct cardiac effect possibly involving the ATP-dependent potassium channel
AUTHOR(S): Chi, Liguu; Black, Shawn C.; Kuo, Philip I.; Fagbemi, S. Oluwole; Lucchesi, Benedict R.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109-0626, USA
SOURCE: J. Cardiovasc. Pharmacol. (1993), 21(2), 179-90
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the ATP-dependent K⁺ channel antagonist glyburide and the ATP-dependent K⁺ channel agonist pinacidil were investigated in a Langendorff-perfused rabbit isolated heart subjected to a period of global hypoxia. A class III antiarrhythmic drug, E-4031, also was studied in

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this model. These studies aimed to define the mechanism of action of putative profibrillatory actions of pinacidil and the mechanism for the antifibrillatory effect of the class III antiarrhythmic drug, E-4031, in the hypoxic heart. After stabilization and detn. of baseline functional parameters under normoxic perfusion conditions (95% O₂/5% CO₂), hearts were subjected to global hypoxia by switching to a 95% N₂/5% CO₂ satd. perfusion medium for a period of 12 min. After the hypoxic period, normoxia was re-established by switching to the oxygen-carbon dioxide satd. buffer medium for a period of 40 min. The oxygen tension of the perfusion buffer was reduced from approx. 400 mm Hg to below 50 mm Hg during the hypoxic period. All hearts subjected to hypoxia had reduced function: the left ventricular developed pressure and \pm dp/dt were reduced significantly. Myocardial tissue ATP concns. were reduced (>50%) in hearts subjected to hypoxia. Under conditions of hypoxic/reoxygenation and in the presence of a low (2.5 mM) potassium concn. ([K⁺]₀), pinacidil (1.25 μ M) facilitated the induction of ventricular fibrillation (80% fibrillation in the presence of pinacidil vs. 20% in the absence of pinacidil). Glyburide (10 μ M) and E-4031 (1 and 10 μ M) significantly reduced the incidence of ventricular fibrillation assocd. with pinacidil (20% fibrillation in the presence of hypoxia, pinacidil, and glyburide or 10 μ M E-4031). Opening of the ATP-dependent K⁺ channel by pinacidil under normoxia and low K⁺ also facilitated the induction of ventricular fibrillation (60% ventricular fibrillation). Pinacidil failed to induce ventricular fibrillation under either normoxic or conditions of hypoxic/reoxygenation when the [K⁺]₀ was increased to 5.1 mM. The results of this study demonstrate that K⁺ channel activators facilitate the induction of ventricular fibrillation under both normoxic conditions and conditions of hypoxic/reoxygenation when the perfusion buffer K⁺ concn. is reduced.

IT **113559-13-0**, E4031

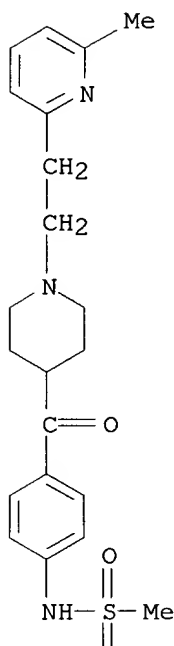
RL: BIOL (Biological study)

(in protection against ischemia and reperfusion-induced ventricular fibrillation, ATP-dependent potassium channel in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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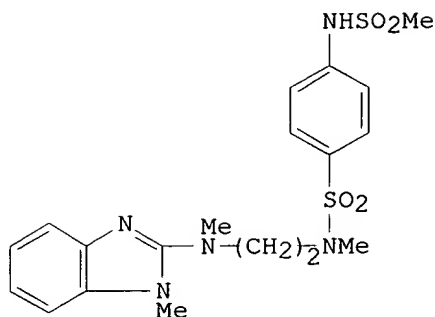
PAGE 2-A



● 2 HCl

L14 ANSWER 148 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:73400 HCAPLUS
DOCUMENT NUMBER: 118:73400
TITLE: Effects of WAY-123398, a new class III antiarrhythmic agent, on cardiac refractoriness and ventricular fibrillation threshold in anesthetized dogs: a comparison with UK-68798, E-4031, and dl-sotalol
AUTHOR(S): Spinelli, Walter; Parsons, Roderick W.; Colatsky, Thomas J.
CORPORATE SOURCE: Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
SOURCE: J. Cardiovasc. Pharmacol. (1992), 20(6), 913-22
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

Searched by Thom Larson, STIC, 308-7309



AB Previous studies in isolated ventricular myocytes showed that WAY-123398 (I) is a selective blocker of the delayed rectifier K⁺ current (I_K). In this report, we studied the electrophysiol. and hemodynamic effects of I in open-chest anesthetized dogs. I prolonged atrial and ventricular refractoriness without affecting conduction; I was as effective as UK-68798, E-4031, and dl-sotalol, but less potent than UK-68798 and E-4031. The increase in atrial refractoriness was approx. twice as large as the ventricular increase with all compds. The hemodynamic effects of I were similar to those of UK-68798; at the ED₂₀ for increasing ventricular refractoriness, I did not affect the mean arterial pressure and decreased the heart rate by 20%. In a different series of expts., all four compds. produced large and comparable increases in the ventricular fibrillation threshold in anesthetized dogs; I and UK-68798 induced defibrillation and restoration of sinus rhythm in two of six dogs each and E-4031 in one of six dogs. No episodes of drug-induced restoration to sinus rhythm were obsd. in dogs treated with sotalol or vehicle. Thus, I is an effective Class III agent without Class I actions and with a favorable hemodynamic profile.

IT **113559-13-0**, E4031

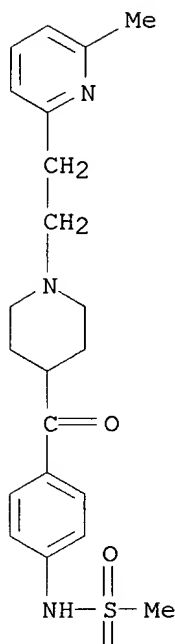
RL: BIOL (Biological study)

(antiarrhythmic, cardiac refractoriness and ventricular fibrillation threshold response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 149 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:52178 HCAPLUS

DOCUMENT NUMBER: 118:52178

TITLE: Differential effects of the new class III antiarrhythmic agents almokalant, E-4031 and D-sotalol, and of quinidine, on delayed rectifier currents in guinea pig ventricular myocytes

AUTHOR(S): Wettwer, Erich; Grundke, Martin; Ravens, Ursula

CORPORATE SOURCE: Pharmakol. Inst., Univ.-Gesamthochsch.-Essen, Essen, D-4300/1, Germany

SOURCE: Cardiovasc. Res. (1992), 26(11), 1145-52

CODEN: CVREAU; ISSN: 0008-6363

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of almokalant (4-[3-ethyl[3-(propylsulfinyl)propyl]amino]-2-hydroxypropoxy]benzonitrile), E-4031 (1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methylsulfonylaminobenzoyl)piperidine), D-sotalol, and quinidine were

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investigated on the delayed K⁺ rectifier current I_K. The aim of the study was to compare the drug action on the two components of this current. Membrane currents were measured in ventricular myocytes from guinea pig hearts with the whole cell voltage clamp technique. I_K was activated during clamp steps from a holding potential of -40 mV to test potentials between -30 and +50 mV. The tail current I_{tail} was measured upon stepping back to holding potential. In control expts., I_K and I_{tail} declined spontaneously ("run down"). With 300 ms long test pulses to +50 mV, only D-sotalol (10⁻⁴ M) caused a significant further decrease in I_K, whereas all four agents significantly reduced I_{tail} (almokalant 10⁻⁶ M, E-4031 10⁻⁷ M, quinidine 10⁻⁵ M). When tested with 1 s long clamp steps at various potentials almokalant (3 .times. 10⁻⁶ M), E-4031 (10⁻⁶ M), quinidine (10⁻⁵ M), and D-sotalol (10⁻⁴ M) reduced I_K in the potential range between -20 and +40 mV, yielding a bell shaped inward rectifying drug sensitive current. I_{tail} was reduced by almokalant and E-4031 over the whole voltage range with satn. of block pos. to +20 mV. Similar redns. with quinidine but not with D-sotalol were also significant. With rest pulses to +50 mV of increasing duration (25 ms-4000 ms), I_{tail} developed with a faster time course than I_K and therefore the ratio of I_{tail}/I_K declined with pulse duration. With almokalant and E-4031, this ratio became independent of test pulse duration. For 250 ms pulses, I_{tail}/I_K was also significantly reduced by D-sotalol and quinidine. Inhibition of the rapidly activating inwardly rectifying component of I_K is prominent with almokalant and E-4031 and less pronounced with D-sotalol and quinidine. Since inhibition of this component prolongs the cardiac action potential, it should contribute to the antiarrhythmic properties of the agents.

IT 113559-13-0, E-4031

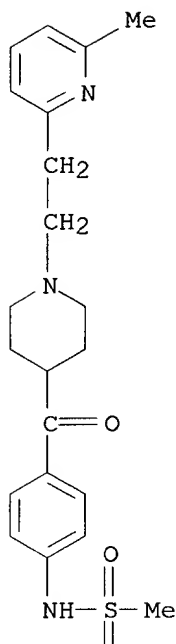
RL: BIOL (Biological study)

(heart delayed potassium rectifier channel inhibition by, action potential prolongation and antiarrhythmic activity in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 150 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:625970 HCAPLUS
DOCUMENT NUMBER: 117:225970
TITLE: Vascular effects of class III antiarrhythmic agents
AUTHOR(S): Baskin, Elizabeth; Serik, Carolann; Wallace, Audrey;
Jurkiewicz, Nancy; Winkquist, Raymond; Lynch, Joseph,
Jr.
CORPORATE SOURCE: Dep. Pharmacol., Merck Res. Lab., West Point, PA,
19486, USA
SOURCE: Drug Dev. Res. (1992), 26(4), 481-8
CODEN: DDREDK; ISSN: 0272-4391
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methanesulfonanilide Class III antiarrhythmic agents have been shown to
block a specific outward delayed rectifier K⁺ current, I_{Kr}, in cardiac
cells. K⁺ conductance also is recognized to be an important regulator of
contractile tone in vascular smooth muscle. The purpose of the present
investigation was to assess the effects of the new and potent

Searched by Thom Larson, STIC, 308-7309

methanesulfonanilide Class III agents E-4031, UK-68,798, UK-66,914 and the Class III std. d-sotalol in vitro in phasically active and elec. quiescent vascular smooth muscle preps. All four Class III agents augmented phasic contractile tension in spontaneously active rat portal veins at concns. similar to those effecting significant Class III electrophysiol. activity in cardiac muscle, but failed to contract elec. quiescent rabbit aortic rings. At concns. exceeding effective cardiac Class III electrophysiol. concns., E-4031 relaxed methoxamine- and histamine-contracted rabbit aortic rings, and d-sotalol relaxed methoxamine-contracted aortic rings. UK-68,798 and UK-66,914 failed to relax spasmogen-contracted aortic rings. The similarity in effective concns. required for the four Class III agents to augment phasic contractile tension in the rat portal vein and increase myocardial refractoriness in cardiac muscle is consistent with the presence of similar K⁺ channel subtypes in the two tissues. Alternatively, the obsd. activities in the two tissues may be due to actions of these four Class III agents on another, non- I_{Kr} ion channel present in rat portal vein, with an order of potency for blockade similar to block of I_{Kr} in cardiac tissue.

IT **113559-13-0**, E-4031

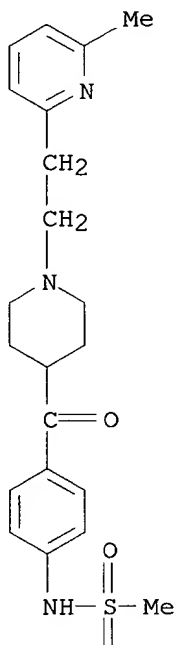
RL: BIOL (Biological study)

(blood vessel contraction response to, potassium channel modulation of)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



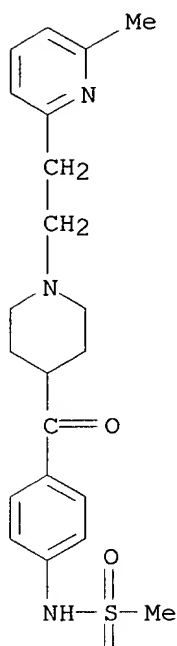
PAGE 2-A

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●2 HCl

L14 ANSWER 151 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:503866 HCAPLUS
DOCUMENT NUMBER: 117:103866
TITLE: Contribution of delayed rectifier and inward rectifier
to repolarization of the action potential:
pharmacologic separation
AUTHOR(S): Martin, Cynthia Lee; Chinn, Kevin
CORPORATE SOURCE: Cardiovasc. Dis. Res., Searle Res. Dev., Skokie, IL,
USA
SOURCE: J. Cardiovasc. Pharmacol. (1992), 19(5), 830-7
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Outward potassium (K) currents contribute to the repolarization process of
cardiac action potentials. There are, however, multiple K currents.
Recently, two putatively specific K channel blockers have been developed
as potential class III antiarrhythmic agents. E-4031 appears to block
specifically a fast component of the delayed rectifier (Ik), and RP 58866
is a reported inward rectifier current (Ik1) blocker. In the present
expts., the authors examd. the effects of E-4031 and RP 58866 on action
potentials recorded from guinea pig papillary muscles to det. whether the
properties of Ik and Ik1 measured in whole-cell expts. would be manifested
in distinct effects. Both compds. prolonged the APD50 (action potential
duration at 50% repolarization) and APD90 (action potential duration at
90% repolarization). However, RP 58866 did not significantly prolong the
action potential at voltages of 0 mV and above, while E-4031 did. The
results suggest that preferential Ik1 block results in a change in action
potential waveform that is distinct from that resulting from block of
other outward K currents. This could thus be used as a simple first-pass
screening tool in detg. a preliminary mechanism of action of class III
antiarrhythmics prior to more time-consuming but necessary whole-cell
voltage clamp expts.
IT 113559-13-0, E-4031
RL: BIOL (Biological study)
(heart action potential and potassium currents response to)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



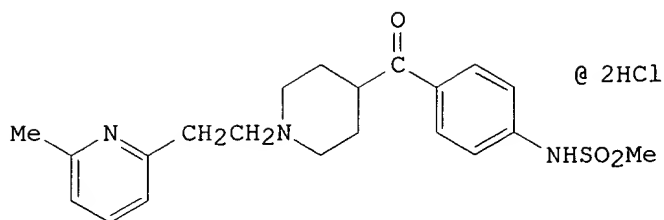
PAGE 2-A



● 2 HCl

L14 ANSWER 152 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:440097 HCAPLUS
DOCUMENT NUMBER: 117:40097
TITLE: Effect of E-4031, a class III antiarrhythmic agent, on experimental infarct size in a canine model of myocardial ischemia-reperfusion injury
AUTHOR(S): Holahan, Marie A.; Stranieri, Maria T.; Stabilito, Inez I.; Lynch, Joseph J., Jr.
CORPORATE SOURCE: Dep. Pharmacol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: J. Cardiovasc. Pharmacol. (1992), 19(6), 892-8
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

Searched by Thom Larson, STIC, 308-7309



AB Class III antiarrhythmic agents such as E-4031 (I) have demonstrated efficacy in preventing and/or terminating malignant ventricular arrhythmias in exptl. models. It has recently been suggested that Class III agents might possess addnl. anti-ischemic properties that may translate into a redn. in the frequency or severity of arrhythmia. The potential for the Class III antiarrhythmic agent E-4031 to limit the extent of developing myocardial infarction was assessed in a barbiturate-anesthetized canine model of ischemic-reperfusion injury. Untreated control and E-4031-treated animals (300 .mu.g/kg, i.v., immediately preceding myocardial ischemia) were subjected to a 90-min period of left circumflex coronary artery occlusion followed by a 5-h period of reperfusion. The predominant hemodynamic effect displayed by E-4031 was a redn. in heart rate throughout the period of coronary artery occlusion and early reperfusion. Areas at risk of infarction, expressed as percentages of left ventricle, were equiv. in the control and E-4031 treatment groups (38.5 and 34.6 %, resp.). Posterolateral myocardial infarct sizes, expressed either as percentages of risk area or of total left ventricle, were reduced slightly but not significantly in the E-4031 treatment group compared to the control group. Regional myocardial blood flows in nonischemic and central ischemic zones of myocardium did not differ significantly between the control and E-4031 treatment groups before and during the period of coronary artery occlusion. Ischemic collateral regional myocardial blood flow/infarct size regression relationships did not differ significantly between the two treatment groups, again suggesting no significant difference in infarct size for a given value of collateral blood flow. These findings suggest that the antiarrhythmic activity displayed by E-4031, particularly in exptl. models of previous myocardial infarction, is likely due to the direct electrophysiol. properties of the drug rather than to indirect cardioprotective actions.

IT **113559-13-0**, E-4031

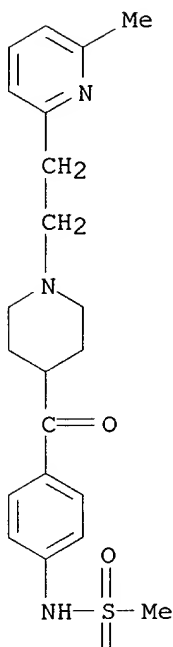
RL: BIOL (Biological study)

(infarct size response to, in myocardial ischemia and reperfusion)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



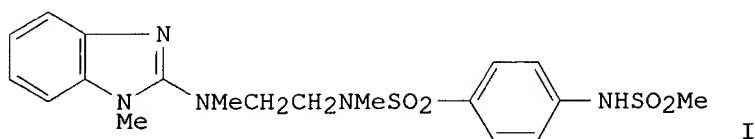
PAGE 2-A



● 2 HCl

L14 ANSWER 153 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:99050 HCAPLUS
DOCUMENT NUMBER: 116:99050
TITLE: Class III antiarrhythmic activity of novel substituted
4-[(methylsulfonyl)amino]benzamides and sulfonamides
AUTHOR(S): Ellingboe, John W.; Spinelli, Walter; Winkley, Michael
W.; Nguyen, Thomas T.; Parsons, Roderick W.; Moubarak,
Issam F.; Kitzen, Jan M.; Von Engen, Donna; Bagli,
Jehan F.
CORPORATE SOURCE: Div. Explor. Chem., Wyeth-Ayerst Res., Princeton, NJ,
08543-8000, USA
SOURCE: J. Med. Chem. (1992), 35(4), 705-16
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

Searched by Thom Larson, STIC, 308-7309



AB The synthesis and Class III antiarrhythmic activity of series of 4-[(methylsulfonyl)amino]benzamides and sulfonamides are described. Selected compds. show a potent Class III activity and are devoid of effects on conduction both in vitro (dog Purkinje fibers) and in vivo (anesthetized dogs). Compds. having 2-aminobenzimidazole group were the most potent, and one compd. having this heterocycle (WAY-123,3980 (I) was selected for further characterization. I was shown to have good oral bioavailability and a favorable hemodynamic profile to produce a 3-fold increase of the ventricular fibrillation threshold and to terminate ventricular fibrillation, restoring sinus rhythm in anesthetized dogs. Voltage-clamp studies in isolated myocytes show that I is a potent and specific blocker of the delayed rectifier K current (IK) at concns. that cause significant prolongation of action potential duration.

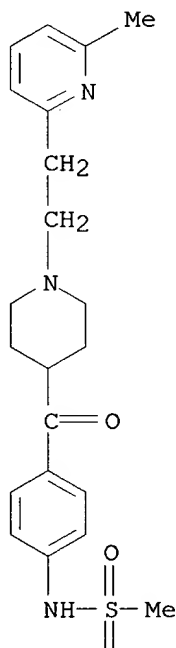
IT **113559-13-0**, E4031

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiarrhythmic activity of, arylbenzamides and sulfonamides in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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●2 HCl

L14 ANSWER 154 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:34157 HCAPLUS

DOCUMENT NUMBER: 116:34157

TITLE: Effects of antiarrhythmic drugs on canine atrial flutter due to reentry: role of prolongation of refractory period and depression of conduction to excitable gap

AUTHOR(S): Inoue, Hiroshi; Yamashita, Takeshi; Nozaki, Akira; Sugimoto, Tsuneaki

CORPORATE SOURCE: 2nd Dep. Intern. Med., Tokyo Univ. Hosp., Tokyo, 113, Japan

SOURCE: J. Am. Coll. Cardiol. (1991), 18(4), 1098-104

CODEN: JACCDI; ISSN: 0735-1097

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Antiarrhythmic drugs prolong the effective refractory period and depress conduction. To det. the exact role played by these 2 electrophysiol. effects in the termination of reentry, the effects of disopyramide, flecainide, propafenone and E-4031, a new class III drug, were examd. in a canine model of atrial flutter (cycle length 20 to 131 ms) caused by reentry. Atrial flutter was induced in 32 anesthetized open chest dogs after placement of an intercaval crush. The excitable gap range from 9 to 11% of the basic flutter cycle length. The effective refractory period in the reentrant circuit during atrial flutter was estd. by subtracting the excitable gap from the basic flutter cycle length. Prolongation of flutter cycle length by the test drugs was proportional to the interatrial conduction time ($r = 0.87$, $p < 0.001$). Atrial flutter was terminated by each test drug in all dogs except for flecainide and propafenone in one dog each. E-4031 prolonged the refractory period during atrial flutter to 129 ms, which did not differ significantly from the flutter cycle length immediately before termination (134 ms). The refractory period during atrial flutter after injection of the other drugs was shorter than the flutter cycle length before termination of atrial flutter (for example, flecainide 126 vs. 179 ms). These data indicate that E-4031 terminated atrial flutter by abolishing the excitable gap through a greater prolongation of refractoriness relative to a lesser slowing of conduction. The other drugs interrupted atrial flutter by suppressing conduction to a crucial point beyond which propagation of conduction became impossible.

IT 113559-13-0, E-4031

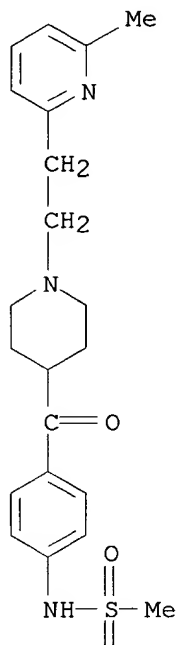
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antiarrhythmic effects of other drugs and, in treatment of atrial flutter, mechanism of)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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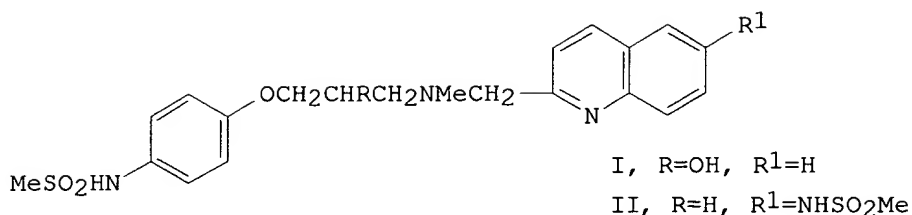


● 2 HCl

L14 ANSWER 155 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1992:34148 HCAPLUS
 DOCUMENT NUMBER: 116:34148
 TITLE: Synthesis and selective class III antiarrhythmic activity of novel N-heteroaralkyl-substituted 1-(aryloxy)-2-propanolamine and related propylamine derivatives
 AUTHOR(S): Butera, John A.; Spinelli, Walter; Anantharaman, Viji; Marcopulos, Nicholas; Parsons, Roderick W.; Moubarak, Issam F.; Cullinan, Catherine; Bagli, Jehan F.
 CORPORATE SOURCE: Div. Explor. Chem. Cardiovasc. Pharmacol., Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
 SOURCE: J. Med. Chem. (1991), 34(11), 3212-28
 CODEN: JMCMAR; ISSN: 0022-2623
 DOCUMENT TYPE: Journal

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English
GI



AB The synthesis and biol. evaluation of a series of novel 1-(aryloxy)-2-propranolamines and several related deshydroxy analogs are described. The compds. were prepd. and investigated for their class III electrophysiol. activity in isolated canine Purkinje fibers and in anesthetized open-chest dogs. None of these compds. showed any class I activity. On the basis of the in vitro data, structure-activity relations for the series are discussed. Two compds., WAY-123,223 (I) and WAY-125,971 (II) were identified and characterized as potent and specific class III antiarrhythmic agents in vitro and in vivo. I was orally bioavailable, to produce large increases of ventricular fibrillation threshold (VFT), and, in some instances, to restore sinus rhythm from ventricular fibrillation in anesthetized open-chest dogs at a dose of 5 mg/kg (i.v.). The enantiomers of I were synthesized and found to exhibit similar electrophysiol. effects in the Purkinje fiber screen. II, a propylamine analog with potency and efficacy comparable to those of UK-68798 and E-4031, was studied in voltage-clamp expts. (isolated cat myocytes) and found to be a potent and specific blocker of the delayed rectifier potassium current (IK).

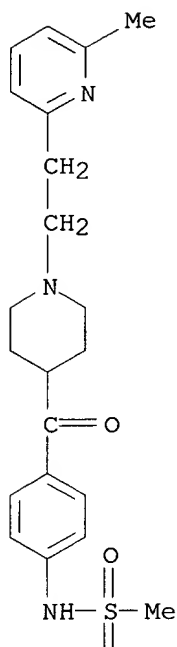
IT **113559-13-0**

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiarrhythmic activity of, heteroaralkyl- and aryloxypropranolamine derivs. in relation to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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● 2 HCl

L14 ANSWER 156 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:670357 HCAPLUS
DOCUMENT NUMBER: 115:270357
TITLE: Cardiac electrophysiologic and inotropic actions of
new and potent methanesulfonanilide class III
antiarrhythmic agents in anesthetized dogs
AUTHOR(S): Wallace, Audrey A.; Stupienski, Raymond F., III;
Brookes, Lynne M.; Selnick, Harold G.; Claremon, David
A.; Lynch, Joseph J., Jr.
CORPORATE SOURCE: Dep. Pharmacol., Merck, Sharp and Dohme Res. Lab.,
West Point, PA, 19486, USA
SOURCE: J. Cardiovasc. Pharmacol. (1991), 18(5), 687-95
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of cumulative i.v. administration of potent and selective
methanesulfonanilide class III antiarrhythmic agents on cardiac
electrophysiol. and hemodynamic parameters were compared with those of

Searched by Thom Larson, STIC, 308-7309

D-sotalol in chloralose-anesthetized dogs. The agents produced dose-dependent increases in ventricular refractoriness, with EDs required to increase the ventricular relative refractory period 20 ms above baseline (ED₂₀, .mu.g/kg i.v.) of 5.2 for UK-68,798, 17 for E-4031, 75 for UK-66,914, and 3700 for D-sotalol. The increases in the electrocardiog. QT and QTc intervals paralleled the increases in ventricular refractoriness for the agents. Increases in left ventricular (LV) + dP/dt also paralleled increases in the ventricular refractoriness and QT intervals for E-4031, and UK-68,798, but not for D-sotalol. No concomitant alterations in LV-dP/dt were obsd. which resulted in increases in the ratio of LV + dP/dt to -dP/dt for E-4031, UK-66,914, and UL-68,798. The agents may augment cardiac contractility in addn. to prolonging ventricular refractoriness.

IT **113559-13-0**, E-4031

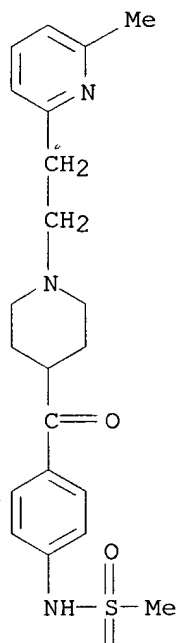
RL: PRP (Properties)

(antiarrhythmic and electrophysiol. effects of, in heart)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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2 HCl

L14 ANSWER 157 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:647804 HCAPLUS

DOCUMENT NUMBER: 115:247804

TITLE: Effect of potassium channel blockade on the anti-ischemic actions of mechanistically diverse agents

AUTHOR(S): Sargent, Carol A.; Smith, Mark A.; Dzwonczyk, Steve; Sleph, Paul G.; Grover, Gary J.

CORPORATE SOURCE: Dep. Pharmacol., Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543, USA

SOURCE: J. Pharmacol. Exp. Ther. (1991), 259(1), 97-103

CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The ATP-sensitive potassium channel opener cromakalim protects ischemic hearts and its effect can be reversed by glyburide. Glyburide may abolish the anti-ischemic effects of mechanistically different agents and blockers of other potassium channels may abolish the protective effects of cromakalim. The effects of glyburide on the activity of cardioprotective agents were tested in globally ischemic/reperfused isolated rat hearts. Calcium antagonists, sodium channel blockers, and calmodulin antagonists improved post-ischemic contractile functions and reduced lactate dehydrogenase release after 25 min of global ischemia and 30 min of reperfusion. Glyburide did not reverse their cardioprotective effects. 5-(N,N-Dimethyl)amiloride, an inhibitor of Na⁺/H⁺ exchange, reduced the lactate dehydrogenase release without improving the post-ischemic contractile function, and glyburide did not reverse this. The potassium channel opener cromakalim protected ischemic rat hearts (improved recovery of contractile function and reduced enzyme release) and this was abolished by glyburide. Charybdotoxin blocked both calcium-activated and voltage-gated potassium channels, and E-4031 blocked the delayed rectifier potassium channels. Neither altered the action of the potassium channel opener cromakalim. Glyburide is selective in that it only blocks the anti-ischemic effects of potassium channel openers and not other cardioprotective compds. Cromakalim action is unaffected by blockers of other potassium channels, further indicating the selectivity of glyburide for ATP-sensitive potassium channels.

IT 113559-13-0, E-4031

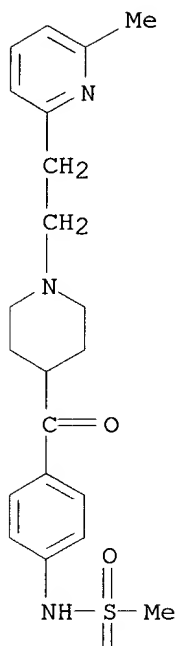
RL: BIOL (Biological study)

(heart ischemia damage prevention by, cardioprotective drugs interaction with)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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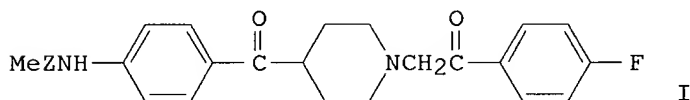


●2 HCl

L14 ANSWER 158 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:607862 HCAPLUS
DOCUMENT NUMBER: 115:207862
TITLE: Preparation of 1-(4-fluorophenyl)-2-[4-(4-substituted benzoyl)piperidino]ethanones as serotonin (5HT₂) antagonists
INVENTOR(S): Carr, Albert A.; Li, Tung; Dudley, Mark W.; Dage, Richard C.; Miller, Francis P.; Koerner, John E.; Nieduzak, Thaddeus R.
PATENT ASSIGNEE(S): Merrell Dow Pharmaceuticals, Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

Searched by Thom Larson, STIC, 308-7309

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|----------|
| EP 437790 | A2 | 19910724 | EP 1990-124973 | 19901220 |
| EP 437790 | A3 | 19920408 | | |
| EP 437790 | B1 | 19960117 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| ZA 9010144 | A | 19911030 | ZA 1990-10144 | 19901217 |
| FI 9006246 | A | 19910622 | FI 1990-6246 | 19901218 |
| FI 96946 | B | 19960614 | | |
| FI 96946 | C | 19960925 | | |
| AU 9068181 | A1 | 19910627 | AU 1990-68181 | 19901218 |
| AU 635098 | B2 | 19930311 | | |
| JP 04145068 | A2 | 19920519 | JP 1990-411705 | 19901219 |
| JP 2934323 | B2 | 19990816 | | |
| IL 96731 | A1 | 19950629 | IL 1990-96731 | 19901219 |
| CA 2032797 | AA | 19910622 | CA 1990-2032797 | 19901220 |
| NO 9005511 | A | 19910624 | NO 1990-5511 | 19901220 |
| NO 176565 | B | 19950116 | | |
| NO 176565 | C | 19950426 | | |
| CN 1052664 | A | 19910703 | CN 1990-110137 | 19901220 |
| CN 1025853 | B | 19940907 | | |
| HU 210590 | B | 19950529 | HU 1990-8370 | 19901220 |
| AT 133163 | E | 19960215 | AT 1990-124973 | 19901220 |
| ES 2084642 | T3 | 19960516 | ES 1990-124973 | 19901220 |
| US 5500433 | A | 19960319 | US 1995-371063 | 19950110 |
| PRIORITY APPLN. INFO.: | | | US 1989-454497 | 19891221 |
| | | | US 1990-604651 | 19901101 |
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| | | | US 1992-819550 | 19920110 |
| | | | US 1992-930490 | 19920814 |
| | | | US 1993-52848 | 19930426 |
| | | | US 1994-220411 | 19940330 |
| OTHER SOURCE(S): | | | MARPAT 115:207862 | |
| GI | | | | |



AB The title compds. (I; Z = CO, SO₂) and their pharmaceutically acceptable acid addn. salts, which are antithrombotics useful for the treatment of thrombotic illness, variant angina, anorexia nervosa, etc., were prepd. Acylation of AcNHPh by 4-(chlorocarbonyl)piperidine hydrochloride in the presence of AlCl₃ gave N-[4-(piperidinocarbonyl)phenyl]acetamide which in aq. THF was refluxed 1.5 h with 2-chloro-4'-fluoroacetophenone and Na₂CO₃ to give title compd. (I; Z = CO) (II). The latter in dogs at 0.001 mg/kg i.v. prevented cyclic blood flow redn., whereas a known ref. compd. 1-(3-pyridyl)-2-[4-[(4-methanesulfonamidophenyl)carbonyl]piperidino]ethane (III) was ineffective at >0.1 mg/kg i.v. II antagonized 5HT₂ in mice by abolishing 5-methoxy-N,N-dimethyltryptamine-induced heat twitch with IC₅₀ of 0.034 mg/kg i.p. and in vitro antagonized binding of [3H]spiroperidol to 5HT₂ receptors with IC₅₀ of 78 nM. The resp. values

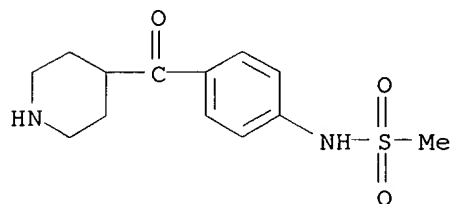
for III were >200 mg/kg i.p. and >5000 nM.

IT **113559-02-7P 124035-23-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and N-alkylation of, by chloro(fluoro)acetophenone, in prepn.
of serotonin antagonist)

RN 113559-02-7 HCAPLUS

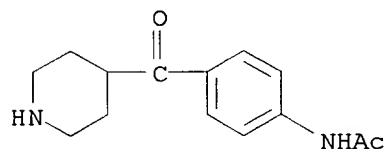
CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 124035-23-0 HCAPLUS

CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]- (9CI) (CA INDEX NAME)

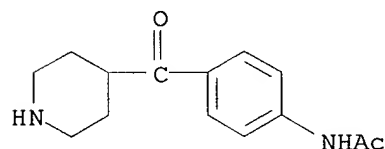


IT **124894-08-2P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 124894-08-2 HCAPLUS

CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride (9CI)
(CA INDEX NAME)



● HCl

L14 ANSWER 159 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:598057 HCAPLUS

DOCUMENT NUMBER: 115:198057

TITLE: Effects of new and potent methanesulfonanilide class

Searched by Thom Larson, STIC, 308-7309

III antiarrhythmic agents on myocardial refractoriness and contractility in isolated cardiac muscle

AUTHOR(S): Baskin, Elizabeth P.; Serik, Carolann M.; Wallace, Audrey A.; Brookes, Lynne M.; Selnick, Harold G.; Claremon, David A.; Lynch, Joseph J., Jr.

CORPORATE SOURCE: Dep. Pharmacol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA

SOURCE: J. Cardiovasc. Pharmacol. (1991), 18(3), 406-14
CODEN: JCPCDT; ISSN: 0160-2446

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of the new and potent methanesulfonanilide class III antiarrhythmic agents E-4031, UK-66,914, and UK-68,798 on myocardial refractoriness and contractility were compared with those of d-sotalol in ferret isometrically contracting right ventricular papillary muscle prepns. During 1-Hz pacing at 37.degree., the 4 class III agents elicited concn.-dependent increases in ventricular effective refractory period (ERP), with a relative order of potency of UK-68,798 > E-4031 > UK-66,914 > d-sotalol. EC25 values (effective concn. required to increase ERP 25% above baseline) were (in .mu.M) UK-68,798, 0.018; E-4031, 0.058; UK-66,914, 0.501; and d-sotalol, 43.76. Maximal percentage increases in ERP relative to baseline for the class III agents at 37.degree. were greater than the maximal increases obsd. at 27.degree., whereas the maximal abs. (ms) increases in ERP above baseline were comparable for the class III agents at both temps. Increases in ERP produced by the 4 agents at 37.degree. were greater at a pacing frequency of 1 Hz than at 3 Hz. During a temporary period of hypoxic perfusion at 37.degree., increases in ERP produced by the agents were reversed, such that "hypoxic" ERP values approximated pretreatment, baseline values. During 1-Hz pacing at 37.degree., modest increases in developed tension, with balanced increases in the rates of tension development and decline, were obsd. with the administrations of E-4031, UK-66,914, and UK-68,798. In contrast, d-sotalol produced minimal effects on myocardial contractility.

IT 113559-13-0, E 4031

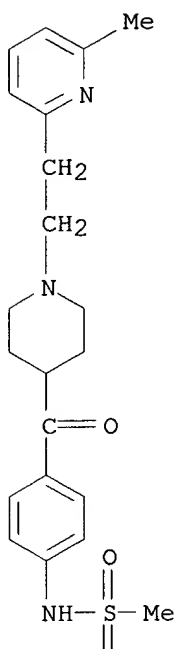
RL: BIOL (Biological study)

(heart contractility and refractoriness response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

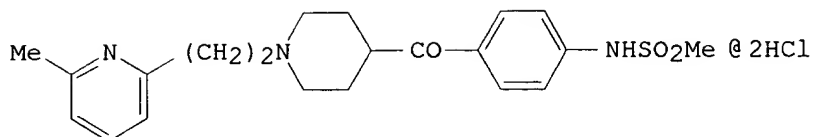


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● 2 HCl

L14 ANSWER 160 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:526693 HCAPLUS
DOCUMENT NUMBER: 115:126693
TITLE: Effects of a new class III antiarrhythmic drug
(E-4031) on canine ventricular arrhythmia models
AUTHOR(S): Hashimoto, K.; Haruno, A.; Matsuzaki, T.; Hirasawa,
A.; Awaji, T.; Uemura, Y.
CORPORATE SOURCE: Dep. Pharmacol., Yamanashi Med. Coll., Yamanashi,
409-38, Japan
SOURCE: Asia Pac. J. Pharmacol. (1991), 6(2), 127-37
CODEN: APJPEV; ISSN: 0217-9687
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB The antiarrhythmic effects of a new class III antiarrhythmic agent, E-4031 (I) were investigated and compared with those of d-sotalol. To det. the antiarrhythmic effects, spontaneously occurring 2-stage coronary ligation-, digitalis- and adrenaline-induced arrhythmias and coronary ligation-reperfusion arrhythmias in dogs were used. E-4031 and d-sotalol did not suppress the 2-stage coronary-ligation arrhythmia and d-sotalol even aggravated the 48 h 2-stage coronary-ligation arrhythmia, while on digitalis-induced arrhythmia models both drugs had no effect. E-4031 aggravated halothane-adrenaline arrhythmia in almost all of the cases, while d-sotalol was almost without effect on this arrhythmia model. E-4031 suppressed the occurrence of fatal ventricular fibrillation in coronary reperfusion arrhythmias, but it induced arrhythmia irresp. of the degree of QT prolongation in these halothane anesthetized dogs before induction of myocardial ischemia. Thus, E-4031 is unique, showing antiarrhythmic effects only on reperfusion arrhythmia and is arrhythmogenic in halothane-anesthetized dogs.

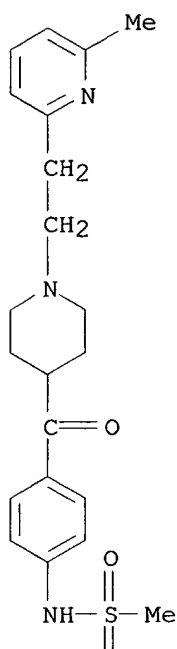
IT **113559-13-0**, E-4031

RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)
(ventricular arrhythmia response to)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 161 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:464412 HCAPLUS
DOCUMENT NUMBER: 115:64412
TITLE: Effects of pentisomide and E-4031 on canine atrial
flutter due to reentry: a comparative study with
disopyramide and propafenone
AUTHOR(S): Inoue, Hiroshi; Yamashita, Takeshi; Usui, Masahiro;
Nozaki, Akira; Saihara, Shinichiro; Sugimoto, Tsuneaki
CORPORATE SOURCE: 2nd Dep. Intern. Med., Tokyo Univ. Hosp., Tokyo, 113,
Japan
SOURCE: J. Cardiovasc. Pharmacol. (1991), 18(1), 137-43
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of new antiarrhythmic drugs, pentisomide (3.5 mg/kg, i.v.), and
E-4031 (5.6 .mu.g/kg), a class III drug, on atrial flutter (AF) caused by
reentry were compared with those of disopyramide (1.6 mg/kg) and
propafenone (2.2 mg/kg). AF was induced with burst atrial pacing after

intercaval crush in anesthetized, open-chest dogs. Termination of AF did not differ among test drugs (8 of 8 with disopyramide, 7 of 8 with propafenone, 6 of 8 with pentisomide, and 8 of 8 with E-4031). Cycle length (CL) of AF was prolonged more with propafenone (57%) and pentisomide (41%) than that with E-4031 (12%). This was also true for the increase in interatrial conduction time detd. at a pacing CL of 150 ms. Increase in the atrial effective refractory period (ERP) detd. at a basic pacing CL of 300 ms did not differ among test drugs. Changes in CL of AF correlated significantly with those in interatrial conduction time, but not with those of ERP. Reinitiation of AF was significantly greater in propafenone (7 of 7) and pentisomide (5 of 6) groups than in disopyramide (1 of 8) and E-4031 (0 of 8) groups. Pentisomide and E-4031 were effective in terminating canine AF due to reentry, as were disopyramide and propafenone. Reinitiation of AF was greater in dogs treated with antiarrhythmic drugs that had more prominent effects on conduction time than on ERP.

IT **113559-13-0**, E-4031

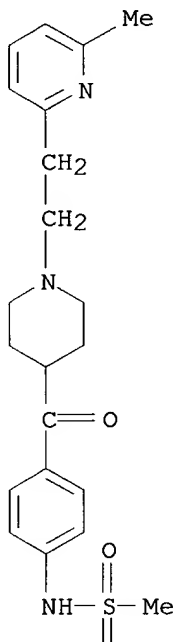
RL: BIOL (Biological study)

(atrial flutter inhibition by)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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O

●2 HCl

L14 ANSWER 162 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:400439 HCAPLUS

DOCUMENT NUMBER: 115:439

TITLE: Antiarrhythmic drugs preferentially produce conduction block at the area of slow conduction in the re-entrant circuit of canine atrial flutter: comparative study of disopyramide, flecainide, and E-4031

AUTHOR(S): Inoue, Hiroshi; Yamashita, Takeshi; Usui, Masahiro; Nozaki, Akira; Sugimoto, Tsuneaki

CORPORATE SOURCE: 2nd Dep. Intern. Med., Tokyo Univ. Hosp., Tokyo, 113, Japan

SOURCE: Cardiovasc. Res. (1991), 25(3), 223-9

CODEN: CVREAU; ISSN: 0008-6363

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim was to test whether antiarrhythmic drugs preferentially suppressed conduction in the area of slow conduction in the re-entrant circuit in anesthetized dogs. I.v. disopyramide [n = 8, plasma concns.: 1.4 (SEM 0.2) .mu.g/mL], flecainide [n = 8, 0.6(0.1) .mu.g/mL], and E-4031, a new class III antiarrhythmic drug [n = 8, 5.6(1.0) ng/mL], were investigated for their effects on atrial flutter due to re-entry in dogs with intercaval crush. In three dogs, detailed atrial activation sequence during atrial flutter was detd. with a hand held bipolar electrode and an epicardial isochronal map was drawn. There was an area of slow conduction during atrial flutter in the low right atrium. Atrial flutter was terminated in all dogs except for one treated with flecainide. In 92% of the dogs, conduction block occurred in the low right atrium in which the area of slow conduction was located. Increase in local conduction time was greater in the area of slow conduction than other parts of the atria (percent ratio to the increase in cycle length of atrial flutter: 63% with disopyramide, 52% with flecainide, and 99% with E-4031). These data suggested antiarrhythmic drugs preferentially suppressed conduction at the area of slow conduction in the re-entrant circuit leading to termination of atrial flutter in this canine model, irresp. of electrophysiol. effects of antiarrhythmic drugs.

IT 113558-89-7

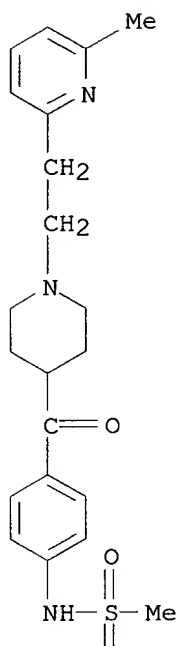
RL: BIOL (Biological study)

(heart elec. activity response to, in ischemia, antiarrhythmic activity in relation to)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

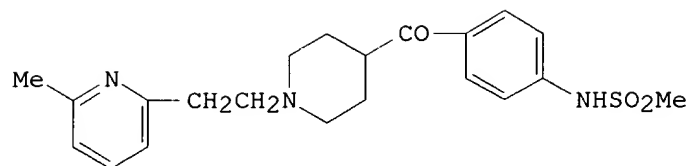
PAGE 1-A



PAGE 2-A



L14 ANSWER 163 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:178113 HCAPLUS
DOCUMENT NUMBER: 114:178113
TITLE: Effects of the new class III antiarrhythmic drug
E-4031 on myocardial contractility and
electrophysiological parameters
AUTHOR(S): Wettwer, Erich; Scholtysik, Guenter; Schaad, Andreas;
Himmel, Herbert; Ravens, Ursula
CORPORATE SOURCE: Pharmakol. Inst., Univ. Gesamthochsch., Essen, Fed.
Rep. Ger.
SOURCE: J. Cardiovasc. Pharmacol. (1991), 17(3), 480-7
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB The effects of the new class III antiarrhythmic agent E-4031 (I) were investigated in different guinea pig cardiac prepns. In left atria, E-4031 (10⁻⁸-10⁻⁵ M) prolonged the functional refractory period up to 45% and reduced the frequency of spontaneously beating right atria by 32%. In papillary muscles, E-4031 (3 .times. 10⁻⁸-3 .times. 10⁻⁷ M) reversibly prolonged the action potential duration (APD70) of fast and slow APs by 68 and 51%, resp. V_{max}, Resting potential, and AP amplitude (APA) were not altered. In isolated ventricular myocytes, E-4031 reversibly prolonged the APD90 from 275 ms (control) to 1,496 ms (10⁻⁶ M), pD₂ value 6.5. The current changes that underlie the AP-prolonging effect were also studied in ventricular myocytes: in concns. up to 10⁻⁵ M, E-4031 did not affect the Na⁺ or Ca²⁺ inward current but reduced the delayed rectifier (I_K) tail current by 76% (10⁻⁷ M). Contractility was enhanced by E-4031 in isolated atria by 20% (3 .times. 10⁻⁷ M) and increased cell shortening in ventricular myocytes. Thus, the class III antiarrhythmic action of E-4031 is due to a selective redn. of outward currents.

IT 113559-13-0, E-4031

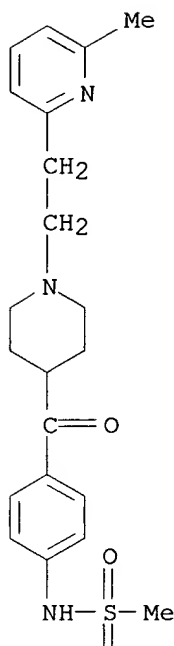
RL: BIOL (Biological study)

(heart contractility and electrophysiol. response to, mechanism of)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



● 2 HCl

L14 ANSWER 164 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:156841 HCAPLUS
DOCUMENT NUMBER: 114:156841
TITLE: Isoproterenol antagonizes prolongation of refractory period by the class III antiarrhythmic agent E-4031 in guinea pig myocytes. Mechanism of action
AUTHOR(S): Sanguinetti, Michael C.; Jurkiewicz, Nancy K.; Scott, Ann; Siegl, Peter K. S.
CORPORATE SOURCE: Dep. Pharmacol., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Circ. Res. (1991), 68(1), 77-84
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism by which isoproterenol (ISO) prevents the prolongation of action potential duration (APD) and refractory period (RP) by the class III antiarrhythmic agent E-4031 was studied. E-4031 (1 .mu.M) increased RP by 50% with no effect on contractile force in papillary muscles

Searched by Thom Larson, STIC, 308-7309

isolated from guinea pig heart. ISO (1 .mu.M) increased force of contraction more than fivefold and decreased RP by 25%. The prolongation of RP by E-4031 was prevented by pretreatment of muscles with ISO. The prolongation of APD in isolated guinea pig ventricular myocytes by 5 .mu.M E-4031 also was antagonized by prior exposure of the cells to 1 .mu.M ISO. Instantaneous currents and delayed rectifier K⁺ currents, I_K, were measured in isolated myocytes using the suction microelectrode voltage-clamp technique. Currents were measured in response to 225-ms depolarizing pulses from a holding potential of -40mV. Previous studies have demonstrated that I_K in these cells results from activation of two distinct outward K⁺ currents, I_{Ks} and I_{Kr} (specifically blocked by E-4031). ISO doubled the magnitude of I_{Ks} without significant effect on I_{Kr}. The instantaneous current, putatively identified as a Cl⁻ current, also was doubled by ISO but was unaffected by E-4031. The augmented conductance of I_{Ks} and instantaneous current by ISO results in a decrease in RP. The small effect of E-4031 on APD and RP in the presence of ISO results from the smaller contribution of I_{Kr} relative to the augmented repolarizing currents.

IT **113559-13-0**, E-4031

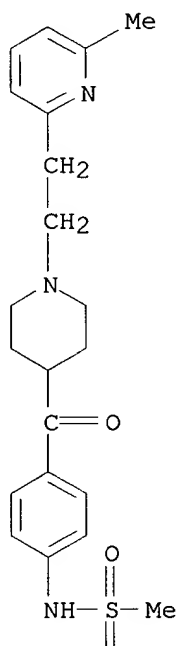
RL: BIOL (Biological study)

(heart action potential duration and refractory period prolongation by, isoproterenol antagonism of)

RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

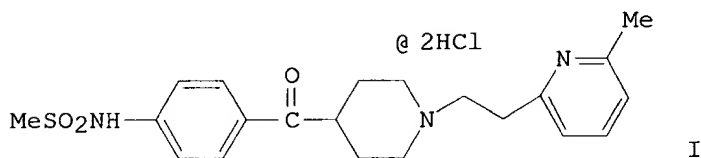


PAGE 2-A



● 2 HCl

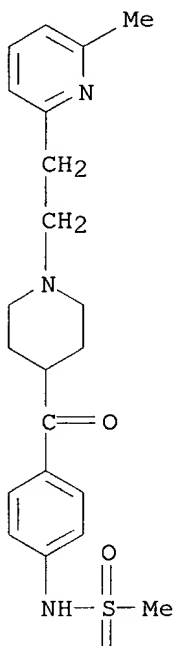
L14 ANSWER 165 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1991:114829 HCAPLUS
 DOCUMENT NUMBER: 114:114829
 TITLE: Electrophysiology and antiarrhythmic actions of E-4031
 in the experimental animal model of sudden coronary
 death
 AUTHOR(S): Chi, Liguu; Mu, Dun Xue; Lucchesi, Benedict R.
 CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109-0626,
 USA
 SOURCE: J. Cardiovasc. Pharmacol. (1991), 17(2), 285-95
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB The Class III agent, E-4031 (I), was evaluated for its antiarrhythmic and antifibrillatory actions in conscious dogs 3-5 days after anterior myocardial infarction that were responsive to the induction of tachyarrhythmia by programmed elec. stimulation. The administration of E-4031 as an i.v. loading dose (100 .mu.g/kg) followed by an infusion for 90 min (10 .mu.g/kg/min) suppressed the induction of ventricular tachycardia by programmedelec. stimulation in 6 to 12 dogs and prolonged the cycle length of the induced arrhythmia in 5 of the 6 remaining animals. Continued administration of E-4031 in a dose regimen of 1,000 .mu.g/kg every 2 h provided significant protection (8 of 10 dogs) against the development of ventricular fibrillation (sudden coronary death) within the 1st hour after the onset of myocardial ischemia in a region of the ventricle remote from the infarct-related vessel. The incidence of sudden coronary death was 80% in a comparable control group of elec. inducible postinfarcted dogs. Increased in ventricular myocardial refractoriness in the paced QT and QTc intervals suggest that Class II electrophysiol. actions contribute to the antiarrhythmic and antifibrillatory actions of E-4031. The findings suggest that E-4031 may be of clin. utility in the prevention of life-threatening arrhythmias in the setting of myocardial ischemia in the postinfarcted heart.

IT 113559-13-0, E 4031
RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)
(electrophysiol. and antiarrhythmic activity of, in exptl. sudden
coronary death)
RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-
piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

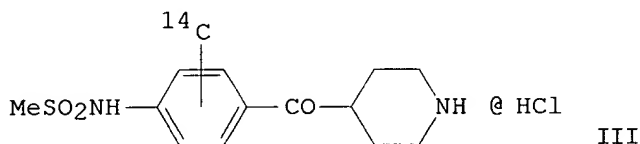
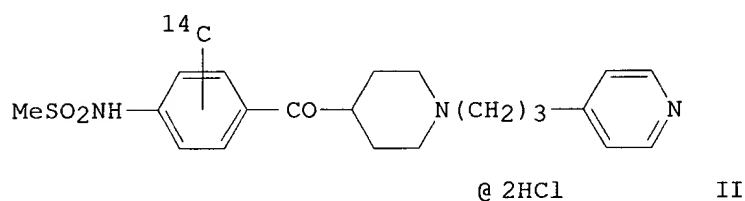
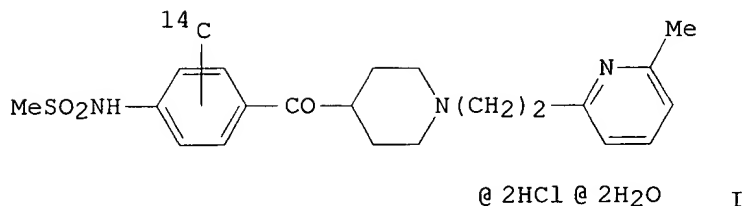


● 2 HCl

L14 ANSWER 166 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:101639 HCAPLUS
DOCUMENT NUMBER: 114:101639
TITLE: Synthesis of antiarrhythmic carbon 14 labeled
[phenyl-14C]4'-[(4-piperidyl)carbonyl]methanesulfonani-
lides
AUTHOR(S): Oinuma, Hitoshi; Miyaka, Kazutoshi; Yamanaka,
Motosuke; Shino, Mitsumasa; Hamano, Sachi-yuki
CORPORATE SOURCE: Tsukuba Res. Lab., Eisai Co., Ltd., Tsukuba, 300-26,

Searched by Thom Larson, STIC, 308-7309

SOURCE: Japan
 J. Labelled Compd. Radiopharm. (1990), 28(8), 921-6
 CODEN: JLCRD4; ISSN: 0362-4803
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



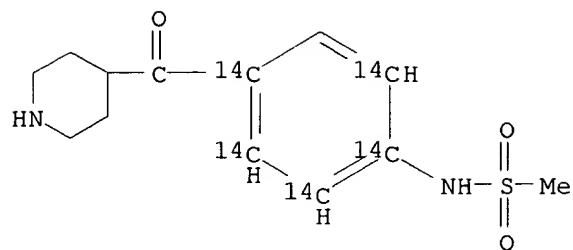
AB Syntheses of selective class III antiarrhythmic agents
 [phenyl- ^{14}C]methanesulfonanilide deriv. (I) and its pyridylpropyl analog
 (II) are described. A modified Michael reaction of [phenyl- ^{14}C]
 sulfonanilide (III) with 6-methyl-2-vinylpyridine, or its alkylation
 with 4-(3-chloropropyl)pyridine produced compds. (I) and (II), resp., in
 satisfactory yields.

IT **132283-89-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and alkylation of, with methylvinylpyridine and
 (chloropropyl)pyridine hydrochloride)

RN 132283-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl- $^{14}\text{C}_6$]-,
 monohydrochloride (9CI) (CA INDEX NAME)



● HCl

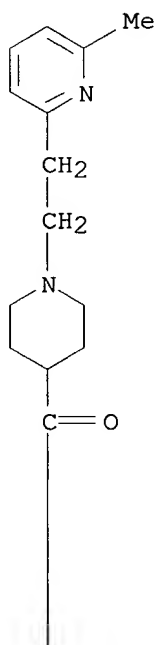
IT 132283-90-0P 132283-91-1P

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

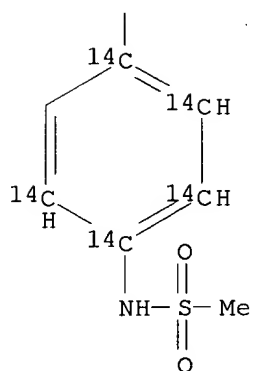
RN 132283-90-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl-14C6]-, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



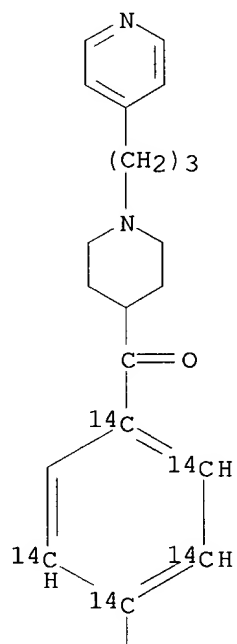
PAGE 2-A



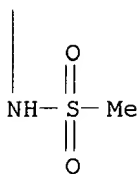
● 2 HCl

RN 132283-91-1 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[3-(4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl- $^{14}\text{C}_6$]-, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

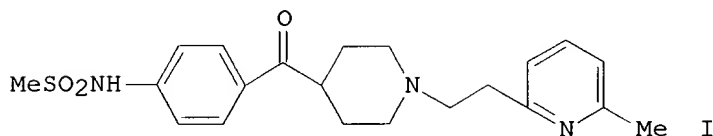


PAGE 2-A



● 2 HCl

L14 ANSWER 167 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:94875 HCAPLUS
DOCUMENT NUMBER: 114:94875
TITLE: Myocardial contractile behavior of a new sotalol derivative
AUTHOR(S): Cingolani, Horacio E.; Wiedmann, Richard T.; Lynch, Joseph J.; Baskin, Elizabeth P.; Stein, Robert B.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, USA
SOURCE: J. Cardiovasc. Pharmacol. (1991), 17(1), 83-9
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB The effects of E4031 (I), a new class III antiarrhythmic agent similar to sotalol, were tested in isometrically contracting rabbit papillary muscles and in anesthetized, open-chest dogs. In papillary muscles, E4031 caused a modest dose-dependent increase of 26% in developed tension and 38% in its maximal rate of rise. Since there was no significant change in the maximal rate of relaxation, the ratio between both maximal velocities increased from 0.92 to 1.19. Time to peak tension did not change significantly, whereas time to half relaxation increased from 72 to 85 ms. The effective refractory period in the rabbit papillary muscles increased from 179 to 414 ms. In the open-chest dog, the i.v. administration of E4031 did not induce changes in heart rate, mean arterial pressure, or left ventricular end diastolic pressure. +DP/dt increased from, 1,839 to 2,470 mm Hg/s with no significant change in -dP/dt after 100 .mu.g/kg of E4031. Consequently, (+dP/dt)/(-dP/dt) increased from 0.97 to 1.18. To further evaluate the effects of E4031 on myocardial relaxation, the time const. of isovolemic left ventricular pressure decay was measured by two different methods (.tau.1 and .tau.2) before and after administering 10 .mu.g/kg E4031. .tau.1 Increased from 27 to 33 ms and .tau.2 increased

from 30 to 41 ms. Apparently, the increase in refractory period and rate-cor. QT (QTc) induced by this compd. suggests a casual link between action potential duration and myocardial relaxation. Whether this effect on relaxation would add advantages or disadvantages to the therapeutic effect of this novel class III antiarrhythmic agent is uncertain at this time.

IT 113558-89-7, E 4031

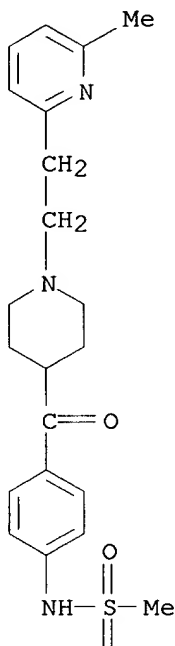
RL: BIOL (Biological study)

(heart contraction and elec. activity response to, as antiarrhythmic)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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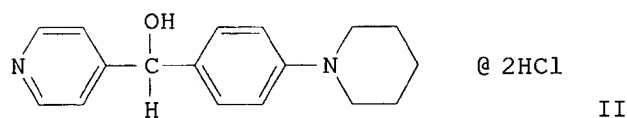
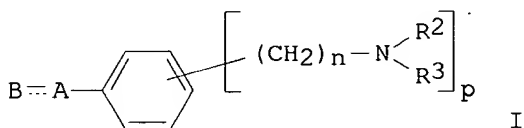
L14 ANSWER 168 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:61935 HCAPLUS
DOCUMENT NUMBER: 114:61935
TITLE: Preparation of cyclic amine drugs
INVENTOR(S): Goto, Giichi; Yukimasa, Hidefumi; Imamoto, Tetsuji
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 65 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

Searched by Thom Larson, STIC, 308-7309

LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 378207 | A1 | 19900718 | EP 1990-100473 | 19900111 |
| EP 378207 | B1 | 19930922 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL | | | | |
| JP 03173867 | A2 | 19910729 | JP 1989-333719 | 19891222 |
| JP 2969359 | B2 | 19991102 | | |
| US 5177087 | A | 19930105 | US 1990-461114 | 19900104 |
| CA 2007553 | AA | 19900713 | CA 1990-2007553 | 19900111 |
| AU 9047911 | A1 | 19900809 | AU 1990-47911 | 19900111 |
| AU 618870 | B2 | 19920109 | | |
| AT 94870 | E | 19931015 | AT 1990-100473 | 19900111 |
| NO 9000174 | A | 19900716 | NO 1990-174 | 19900112 |
| HU 53079 | A2 | 19900928 | HU 1990-118 | 19900112 |
| CN 1053231 | A | 19910724 | CN 1990-100169 | 19900112 |
| CN 1024548 | B | 19940518 | | |
| ZA 9000235 | A | 19910925 | ZA 1990-235 | 19900112 |
| RU 2021989 | C1 | 19941030 | RU 1990-4742823 | 19900112 |
| US 5294625 | A | 19940315 | US 1992-964851 | 19921218 |
| US 5441967 | A | 19950815 | US 1993-171163 | 19931222 |
| FI 9401703 | A | 19940413 | FI 1994-1703 | 19940413 |
| PRIORITY APPLN. INFO.: | | | JP 1989-6651 | 19890113 |
| | | | JP 1989-179495 | 19890712 |
| | | | JP 1989-253162 | 19890928 |
| | | | US 1990-461114 | 19900104 |
| | | | EP 1990-100473 | 19900111 |
| | | | FI 1990-192 | 19900112 |
| | | | US 1992-964851 | 19921218 |

OTHER SOURCE(S): MARPAT 114:61935
 GI



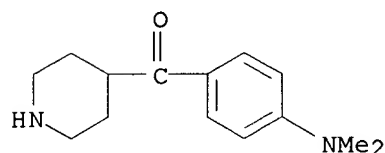
AB Title compds. I [B = (un)satd. 5- to 7-membered azaheterocyclyl; A = bond, (substituted) di- or trivalent hydrocarbonyl; R2, R3 = H, alkyl or NR2R3 = cyclic amino; n = 0-2; p = 1, 2], useful as antihypoxic and antiedematic drugs, were prepd. For example, title compd. II was obtained by reaction of 4-(4-fluorobenzoyl)pyridine with piperidine, followed by catalytic hydrogenation. The antihypoxic activity of II was demonstrated in mice. A 2 mg/kg i.p. dose resulted in a 63% increase in survival time vs. the control group.

IT 131417-51-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of cyclic amine drug)

RN 131417-51-1 HCAPLUS

CN Methanone, [4-(dimethylamino)phenyl]-4-piperidiny- (9CI) (CA INDEX NAME)

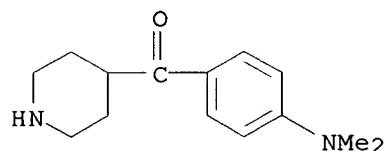


IT **131416-13-2P 131416-60-9P 131417-36-2P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as drug)

RN 131416-13-2 HCAPLUS

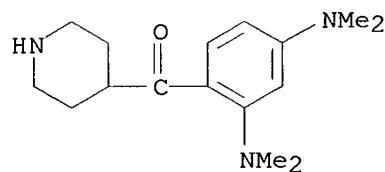
CN Methanone, [4-(dimethylamino)phenyl]-4-piperidiny-, dihydrochloride (9CI)
(CA INDEX NAME)



●2 HCl

RN 131416-60-9 HCAPLUS

CN Methanone, [2,4-bis(dimethylamino)phenyl]-4-piperidiny-, trihydrochloride (9CI) (CA INDEX NAME)



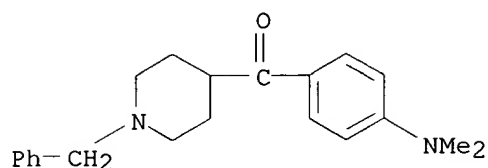
●3 HCl

RN 131417-36-2 HCAPLUS

CN Methanone, [4-(dimethylamino)phenyl][1-(phenylmethyl)-4-piperidiny]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

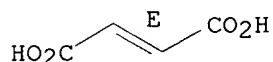
CRN 131417-35-1
CMF C21 H26 N2 O



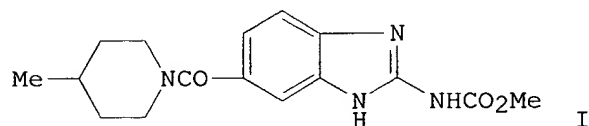
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



L14 ANSWER 169 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:631267 HCAPLUS
DOCUMENT NUMBER: 113:231267
TITLE: Studies in antiparasitic agents. Part 11. Synthesis of 5-substituted 2-alkyl(aryl)carbonylaminobenzimidazoles as orally effective anthelmintics
AUTHOR(S): Naim, S. Shawkat; Singh, Sudhir K.; Sharma, Satyavan; Gupta, Suman; Khan, A. M.; Jain, M. K.; Singh, Som Nath; Chatterjee, R. K.; Katiyar, J. C.
CORPORATE SOURCE: Med. Chem. Div., Cent. Drug Res. Inst., Lucknow, 226 001, India
SOURCE: Indian J. Chem., Sect. B (1990), 29B(5), 464-70
CODEN: IJSBDB; ISSN: 0376-4699
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:231267
GI



AB A series of 2-(acetylamino)-5(6)-substituted benzimidazoles and Me 5(6)-substituted benzimidazole-2-carbamates, e.g. I, were prepd. and evaluated for their antiparasitic, i.e. anthelmintic and antifilaricidal activity. I was effective against *Ancylostoma ceylanicum*, *Nippostrongylus*

brasiliensis, Syphacia obvelata, Hymenolepsis nana, and Cysticercus fasciol in rodents.

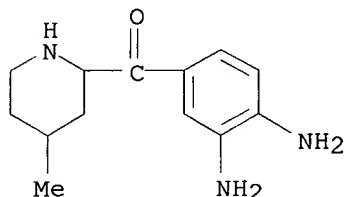
IT 129165-90-8 129165-91-9

RL: RCT (Reactant)

(cyclocondensation reaction of, with cyanogen bromide)

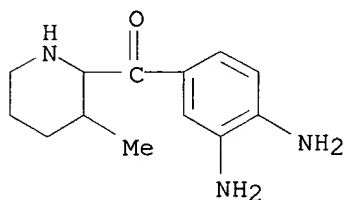
RN 129165-90-8 HCAPLUS

CN Methanone, (3,4-diaminophenyl) (4-methyl-2-piperidiny)- (9CI) (CA INDEX NAME)



RN 129165-91-9 HCAPLUS

CN Methanone, (3,4-diaminophenyl) (3-methyl-2-piperidiny)- (9CI) (CA INDEX NAME)



L14 ANSWER 170 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:624399 HCAPLUS

DOCUMENT NUMBER: 113:224399

TITLE: Negative lusitropic effect of DPI 201-106 and E4031. Possible role of prolonging action potential duration
AUTHOR(S): Cingolani, Horacio E.; Wiedmann, Richard T.; Lynch, Joseph J.; Wenger, Herbert C.; Scott, Ann L.; Siegl, Peter K. S.; Stein, Robert B.

CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, USA
SOURCE: J. Mol. Cell. Cardiol. (1990), 22(9), 1025-34
CODEN: JMCDAJ; ISSN: 0022-2828

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In open-chest anesthetized dogs, the time const. of isovolumic left ventricular pressure decay increased following the i.v. administration of E4031, a class III antiarrhythmic agent which acts by K⁺ channel blockade, or DPI 201-106 (DPI), a cardiotonic agent which acts by delaying Na⁺ channel inactivation. In addn. to prolonging cardiac refractoriness, both E4031 and DPI increased left ventricular +dP/dt but without altering -dP/dt. Consequently, the value of the ratio (+dP/dt)/(-dP/dt) increased. There were no changes in heart rate, mean arterial pressure, or left ventricular end diastolic pressure. Since both E4031 and DPI prolonged the action potential duration (APD) and refractory period and slowed the

relaxation in vivo, the possibility of a causal link between these effects was further investigated under in vitro conditions. In isometrically contracting rabbit papillary muscles, E4031 and DPI increased peak developed tension (DT) and its maximal rate of rise (+.ovrhdot.T). Since the maximal rate of fall of DT (-.ovrhdot.T) did not increase by the same factor that +.ovrhdot.T increased, the value of the ratio +.ovrhdot.T/-.ovrhdot.T increased. Time to half relaxation increased, whereas time to peak tension was not changed by either E4031 or DPI. These neg. lusitropic effects produced by E4031 or DPI were not obsd. when equiv. increases in contractility were produced by increasing the extracellular Ca²⁺ concn. The effective refractory period measured in the papillary muscles increased following superfusion with either of the two drugs, consistent with their known ability to increase APD. A causal link between the prolongation of APD and the neg. lusitropic effects of E4031 and DPI is postulated as the possible mechanism.

IT **113558-89-7**, E-4031

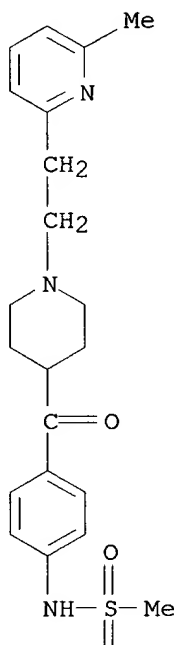
RL: BIOL (Biological study)

(heart action potential and contractility response to)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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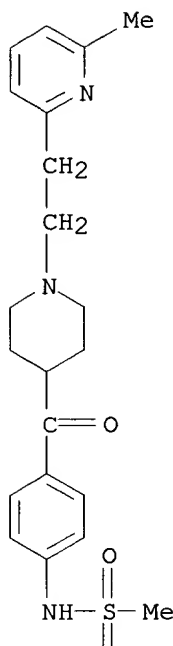


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L14 ANSWER 171 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:565174 HCAPLUS
DOCUMENT NUMBER: 113:165174
TITLE: Two components of cardiac delayed rectifier potassium current. Differential sensitivity to block by class III antiarrhythmic agents
AUTHOR(S): Sanguinetti, Michael C.; Jurkiewicz, Nancy K.
CORPORATE SOURCE: Dep. Pharmacol., Merck, Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: J. Gen. Physiol. (1990), 96(1), 195-215
CODEN: JGPLAD; ISSN: 0022-1295
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The delayed rectifier K⁺ current (I_K) of guinea pig ventricular myocytes results from the activation of 2 outward K⁺ currents. One current was specifically blocked by the benzenesulfonamide antiarrhythmic agent E-4031 (IC₅₀ = 397 nM). The drug-sensitive current I_{Kr} exhibits prominent rectification and activates very rapidly relative to the slowly activating drug-insensitive current I_{Ks}. I_{Ks} was characterized by a delayed onset of activation that occurs over a voltage range typical of the classically described cardiac I_K. Fully activated I_{Ks} was 11.4 times larger than the fully activated I_{Kr}. I_{Kr} was also blocked by d-sotalol (100 μM), a less potent benzenesulfonamide class III antiarrhythmic agent. The activation curve of I_{Kr} had a steep slope (+7.5 mV) and a neg. half-point (-21.5 mV) relative to the activation curve of I_{Ks} (slope = +12.7 mV, half-point = +15.7 mV). The reversal potential (E_{rev}) of I_{Kr} (-93 mV) was similar to E_K (-94 mV for [K⁺]_o = 4 mM), whereas E_{rev} of I_{Ks} was -77 mV. The time consts. for activation and deactivation of I_{Kr} made up a bell-shaped function of membrane potential, peaking between -30 and -40 mV (170 ms). The slope conductance of the linear portion of the fully activated I_{Kr}-V relation was 22.5 S/F. Inward rectification of this relation occurred at potentials > -50 mV, resulting in a voltage-dependent decrease in peak I_{Kr} at test potentials > 0 mV. Peak I_{Kr} at 0 mV averaged 0.8 pA/pF. Although the magnitude of I_{Kr} was small relative to fully activated I_{Ks}, the 2 currents were of similar magnitude when measured during a relatively short pulse protocol (225 ms) at membrane potentials (-20 to +20 mV) typical of the plateau phase of cardiac action potentials.
IT 113558-89-7, E-4031
RL: BIOL (Biological study)
(potassium rectifier currents response to, in heart ventricle, antiarrhythmic effect in relation to)
RN 113558-89-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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L14 ANSWER 172 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:526299 HCAPLUS
 DOCUMENT NUMBER: 113:126299
 TITLE: Block of delayed rectifier potassium current, I_K , by flecainide and E-4031 in cat ventricular myocytes
 AUTHOR(S): Follmer, Christopher H.; Colatsky, Thomas J.
 CORPORATE SOURCE: Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
 SOURCE: Circulation (1990), 82(1), 289-93
 CODEN: CIRCAZ; ISSN: 0009-7322
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Blocks of the delayed rectifier potassium current, I_K , by the class Ic antiarrhythmic agent flecainide and by the novel selective class III antiarrhythmic agent E-4031 were compared in isolated cat ventricular myocytes using the single suction-pipet voltage-clamp technique. Flecainide (10 μ M) markedly reduced I_K elicited on depolarization steps to plateau voltages (+10 mV) and nearly completely blocked the tail currents elicited on repolarization to -40 mV (93% block at +40 mV). E-4031 (1 μ M) produced similar effects (96% block at +40 mV). Slow voltage ramps from -100 to +40 mV confirmed inward rectifying properties of I_K and showed that flecainide and E-4031 have no effects on the background potassium current I_{K1} . Thus, the block of I_K is a common

feature of flecainide and E-4031. IK Block by E-4031 most likely underlies its potent class III antiarrhythmic properties. Flecainide block of IK during an action potential would tend to prolong repolarization, but this effect may be obscured by concomitant block of plateau Na⁺ channels to produce little or no change in action potential duration, consistent with its class Ic classification.

IT 113558-89-7, E-4031

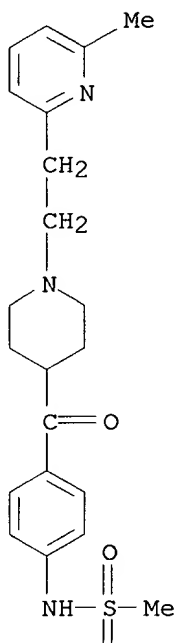
RL: BIOL (Biological study)

(heart potassium currents response to, antiarrhythmic effects in relation to)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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L14 ANSWER 173 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:491179 HCAPLUS

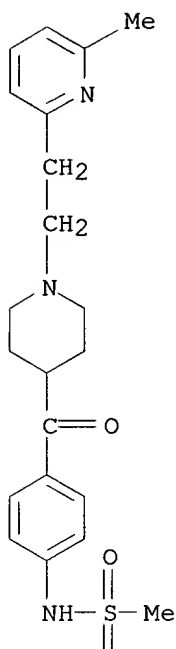
DOCUMENT NUMBER: 113:91179

TITLE: Electrophysiologic effects of E-4031, a class III antiarrhythmic agent, on re-entrant ventricular arrhythmias in a canine 7-day-old myocardial infarction model

AUTHOR(S): Katoh, Hiroshi; Ogawa, Satoshi; Furuno, Izumi; Sato,

Searched by Thom Larson, STIC, 308-7309

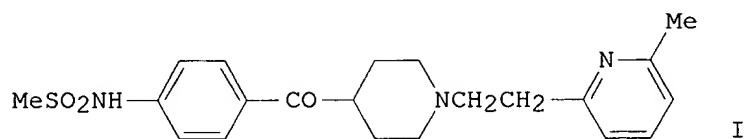
PAGE 1-A



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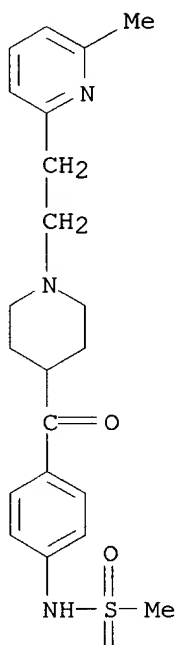
L14 ANSWER 174 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:491160 HCAPLUS
 DOCUMENT NUMBER: 113:91160
 TITLE: Effects of a novel class III antiarrhythmic agent, E-4031, on reentrant tachycardias in rabbit right atrium
 AUTHOR(S): Adaniya, Hitoshi; Hiraoka, Masayasu
 CORPORATE SOURCE: Med. Res. Inst., Tokyo Med. Dent. Univ., Tokyo, 113, Japan
 SOURCE: J. Cardiovasc. Pharmacol. (1990), 15(6), 976-82
 CODEN: JCPCDT; ISSN: 0160-2446
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



Yoshihiro; Yoh, Shisei; Saek, Kimiko; Nakamura, Yoshiro
CORPORATE SOURCE: Sch. Med., Keio Univ., Tokyo, 160, Japan
SOURCE: J. Pharmacol. Exp. Ther. (1990), 253(3), 1077-82
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of E-4031, a class III antiarrhythmic agent, on re-entrant ventricular arrhythmias, were studied in dogs with a 7-day-old myocardial infarction. Epicardial mapping and local refractory periods were obtained using 47-channel bipolar electrodes attached to the epicardium. The induction of sustained ventricular tachycardia by programmed elec. stimulation was not suppressed by i.v. infusion of E-4031 at 1 .mu.g/kg/min in 6 of 7 dogs. During the infusion at 10 .mu.g/kg/min, the epicardial conduction velocity in the normal ventricle did not change (0.70 to 0.71 m/s), whereas the slowed conduction in the infarct zone improved (0.58 to 0.77 m/s). E-4031 at 10 .mu.g/kg/min prolonged the effective refractory periods (ERP) in the normal zone (139 to 164 ms), nontransmural infarct zone (145 to 177 ms), and transmural infarct zone (156 to 191 ms). The degrees of ERP prolongation were almost equal in all zones. On epicardial mapping, the areas of longer ERP and delayed conduction became inexcitable after the administration of E-4031. Thus, E-4031 effectively prevented the induction of re-entrant ventricular tachycardia in the canine myocardial infarction model. E-4031 may render re-entrant circuits inexcitable by marked ERP prolongation in both normal and infarct zones.
IT 113558-89-7, E-4031
RL: BIOL (Biological study)
(heart reentrant arrhythmias and tachycardia inhibition by, after infarction)
RN 113558-89-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

- AB The effects of the new antiarrhythmic agent E-4031 (I) on reentrant types of tachycardias in rabbit right atrial preps. were studied by microelectrode techniques. E-4031 at 0.1 and 1.0 μ M prolonged the refractory period of the atrium and atrioventricular node (AVN) without affecting the intraatrial conduction time. In 13 of 17 preps., premature stimulation repeatedly induced tachycardias lasting >10 beats. Twelve of 13 preps. exhibited a smooth AV conduction curve and showed activation patterns compatible with intraatrial reentry during tachycardias, whereas the remaining prep. started tachycardia with a jump on the AV conduction curve, indicating dual AVN reentrant tachycardia. Addn. of 0.1 and 1.0 μ M E-4031 completely prevented the initiation of both types of tachycardias by producing intraatrial conduction block due to prolonged effective refractory period of the atrium. E-4031, exhibiting pure class III antiarrhythmic properties, is effective for prevention of reentrant type of supraventricular tachycardias.
- IT **113558-89-7**, E-4031
 RL: BIOL (Biological study)
 (heart atrial tachycardia response to)
- RN 113558-89-7 HCAPLUS
- CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

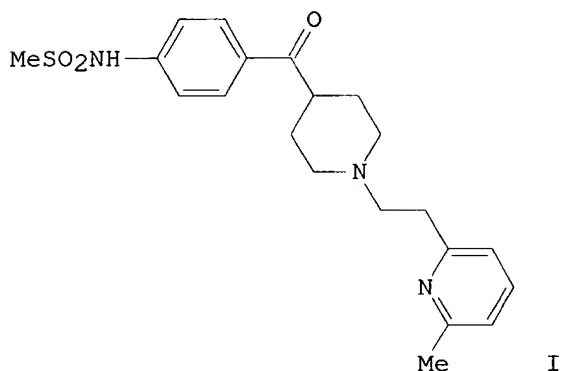
PAGE 1-A



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L14 ANSWER 175 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:417674 HCAPLUS
DOCUMENT NUMBER: 113:17674
TITLE: Suppression of lethal ischemic ventricular arrhythmias
by the class III agent E4031 in a canine model of
previous myocardial infarction
AUTHOR(S): Lynch, Joseph J., Jr.; Heaney, Lisa A.; Wallace,
Audrey A.; Gehret, John R.; Selnick, Harold G.; Stein,
Robert B.
CORPORATE SOURCE: Dep. Pharmacol., Merck, Sharp and Dohme Res. Lab.,
West Point, PA, 19486, USA
SOURCE: J. Cardiovasc. Pharmacol. (1990), 15(5), 764-75
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

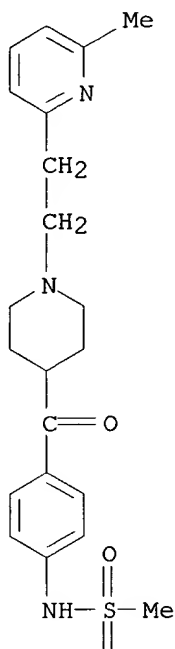


AB The antiarrhythmic efficacy of a new and potent class III agent E4031 (I) piperidine deriv. was evaluated in several canine models of recent myocardial infarction. In anesthetized dogs with baseline inducible ventricular arrhythmias studied 4-10 days after anterior myocardial infarction, 30-300 .mu.g/kg i.v. E4031 suppressed induced of ventricular tachyarrhythmias by programmed ventricular stimulation in 7 of 10 animals tested, while prolonging refractoriness in both noninfarcted and infarcted ventricular myocardium. The incidence of lethal ischemic ventricular arrhythmias developing in response to acute posterolateral myocardial ischemia in the presence of previous anterior infarction was reduced from 10 of 10 in a vehicle pretreatment group to 3 of 10 an E4031 (300 .mu.g/kg i.v.) pretreatment group. The redn. in the incidence of lethal ischemic arrhythmias in the E4031 pretreatment group was not due to smaller underlying, elec. unstable myocardial substrates nor to a delay in onset of the acute ischemic insult. These findings suggest that pharmacol. agents such as E4031 that increase ventricular refractoriness (class III electrophysiol. activity) may provide protection against development of malignant ischemic ventricular arrhythmias in the setting of previous myocardial infarction.

IT 113558-89-7, E4031

RL: BIOL (Biological study)
 (heart ischemic ventricular arrhythmia suppression by)
 RN 113558-89-7 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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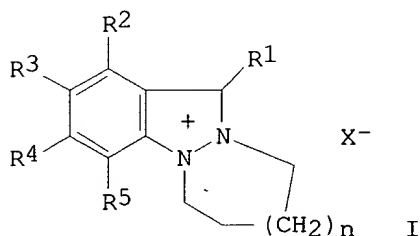


L14 ANSWER 176 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:216936 HCAPLUS
 DOCUMENT NUMBER: 112:216936
 TITLE: Preparation of pyrazolo[1,2-a]indazolium compounds as antiasthmatics
 INVENTOR(S): Grayshan, Roger; French, Andrew McKinnon; Al-Khammees, Hamad; De Boos, Gareth Andrew
 PATENT ASSIGNEE(S): National Research Development Corp., UK
 SOURCE: PCT Int. Appl., 30 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

Searched by Thom Larson, STIC, 308-7309

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|--|-------|-------------------|----------------|----------|
| ----- | ----- | ----- | ----- | ----- |
| WO 8910924 | A1 | 19891116 | WO 1989-GB517 | 19890512 |
| W: JP, US | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| JP 03504242 | T2 | 19910919 | JP 1989-505608 | 19890512 |
| PRIORITY APPLN. INFO.: | | | GB 1988-11299 | 19880512 |
| | | | WO 1989-GB517 | 19890512 |
| OTHER SOURCE(S): | | MARPAT 112:216936 | | |
| GI | | | | |



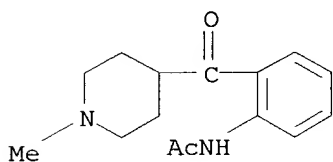
AB Title compds. I [R1 = (un)substituted 6-membered N-heterocyclyl bound to a C to the indazole ring; R2 = H, HO, C1-6 alkyl, C1-6 alkoxy; R3, R4 = H, HO, halo, C1-6 alkyl, -alkoxy, O2N, cyano, H2NCO, RNHCO; R = C1-3 alkyl; R5 = H, halo; X = pharmaceutically acceptable anion; n = 1,2] useful as antiasthmatics (no data), are prepd. 3-(1-Methyl-1,2,5,6-tetrahydro-4-pyridyl)indazole (prepn. given) in DMF was added to NaH in DMF, and the mixt. added to Br(CH2)3Br in DMF to give 2,3-dihydro-9-(1,2,5,6-tetrahydro-1-methyl-4-pyridyl)pyrazole[1,2-a]indazolium bromide which was taken up in BuOH and aq. HCl to give the bromide-HCl.

IT **126971-83-3P 126971-84-4P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (prepn. and reaction of, in prepn. of antiasthmatic pyrazoloindazolium compds.)

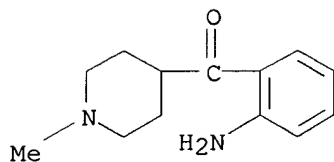
RN 126971-83-3 HCAPLUS

CN Acetamide, N-[2-[(1-methyl-4-piperidyl)carbonyl]phenyl]- (9CI) (CA INDEX NAME)



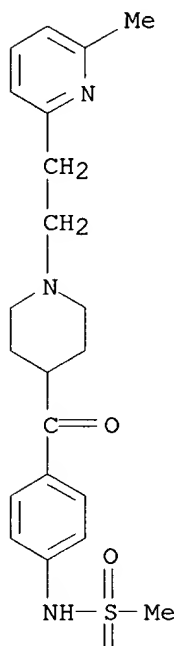
RN 126971-84-4 HCAPLUS

CN Methanone, (2-aminophenyl)(1-methyl-4-piperidyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 177 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:210797 HCAPLUS
 DOCUMENT NUMBER: 112:210797
 TITLE: Electrophysiological effects of E-4031, a class 3 antiarrhythmic agent, on guinea pig ventricular muscle; comparison with the effect of dl-sotalol, in normoxic and ischemic conditions
 AUTHOR(S): Kajita, Junichiro
 CORPORATE SOURCE: Sch. Med., Nihon Univ., Tokyo, Japan
 SOURCE: Nichidai Igaku Zasshi (1990), 49(2), 117-23
 CODEN: NICHAS; ISSN: 0029-0424
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 AB E-4031 (10 .mu.M) prolonged the action potential duration (APD) of guinea pig ventricular muscle under normoxic conditions compared with dl-sotalol (10 .mu.M). E-4031 lengthened the APD during the 1st 5 min of ischemia, whereas there was no difference between the dl-sotalol-treated group and the control group after 5 min of ischemia. Neither of the drugs affected the resting membrane potential, upstroke velocity, and developed tension.
 IT **113558-89-7**, E-4031
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antiarrhythmic activity of, in ischemia)
 RN 113558-89-7 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-(6-methyl-2-pyridinyl)ethyl)]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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L14 ANSWER 178 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:191632 HCAPLUS
DOCUMENT NUMBER: 112:191632
TITLE: Effects of antiarrhythmic agents of class III on
ischemia-induced myocardial damage in canine hearts
AUTHOR(S): Sano, T.; Sugiyama, S.; Taki, K.; Hanaki, Y.; Shimada,
Y.; Ozawa, T.
CORPORATE SOURCE: Fac. Med., Univ. Nagoya, Nagoya, Japan
SOURCE: Br. J. Pharmacol. (1990), 99(3), 577-81
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cardioprotective effects of several antiarrhythmic agents of class
III, amiodarone, sotalol, and E-4031, were investigated in anesthetized
dogs. The left anterior descending coronary artery was occluded for 2 h.
Heart mitochondria were prepd. from both the ischemic and non-ischemic
areas, and their function was estd. polarog. Activities of the lysosomal
enzymes, N-acetyl-.beta.-glucosaminidase and .beta.-glucuronidase, were
measured in each fraction. Two hour occlusion induced ventricular
arrhythmias, and amiodarone, sotalol and E-4031 greatly suppressed the
development of arrhythmias. Amiodarone, sotalol, and E-4031 protected
mitochondria against ischemia, and prevented ischemia-induced leakage of

lysosomal enzymes. Antiarrhythmic agents of class III show cardioprotective effects, which may participate in their antiarrhythmic effect.

IT 113558-89-7, E 4031

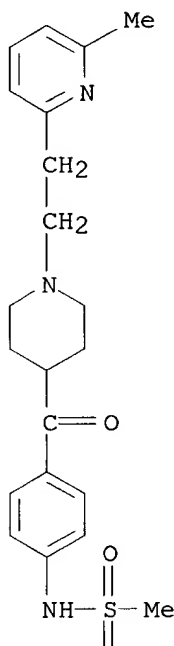
RL: BIOL (Biological study)

(heart ischemia-induced myocardial damage prevention by)

RN 113558-89-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

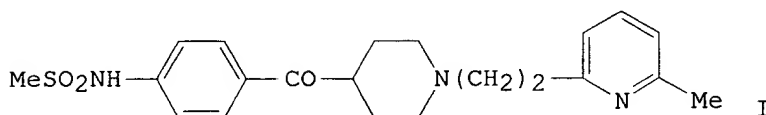


PAGE 2-A



L14 ANSWER 179 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:118616 HCAPLUS
 DOCUMENT NUMBER: 112:118616
 TITLE: 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides as
 potent, selective, bioavailable class III
 antiarrhythmic agents
 AUTHOR(S): Oinuma, Hitoshi; Miyake, Kazutoshi; Yamanaka,
 Motosuke; Nomoto, Kenichi; Katoh, Hiroshi; Sawada,
 Kohei; Shino, Mitsumasa; Hamano, Sachiyuki
 CORPORATE SOURCE: Tsukuba Res. Lab., Eisai, Co., Ltd., Tsukuba, 300-26,
 Japan

SOURCE: J. Med. Chem. (1990), 33(3), 903-5
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:118616
GI



AB In the search for new class III antiarrhythmic agents, a series of a 4'-[(4-piperidiny)carbonyl] methanesulfonanilides, e.g., I, were prepd. Their electrophysiol. and pharmacol. effects were studied in isolated guinea-pig right ventricular papillary muscles and anesthetized dogs, resp. Of these, I was a potent, highly selective class III antiarrhythmic agent and demonstrate significant bioavailability in animals. The class III activity of I was approx. 100 times more potent than that of d-sotalol. The antiarrhythmic effects of I on ventricular fibrillation were also demonstrated in anesthetized coronary ligated dogs (i.v. infusion, 5 .mu.g/kg/min).

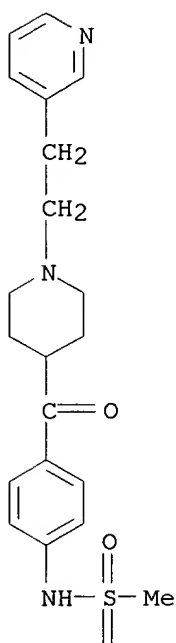
IT **113558-75-1P 113558-89-7P 124536-77-2P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antiarrhythmic activity of)

RN 113558-75-1 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(3-pyridinyl)ethyl]-4-piperidiny]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

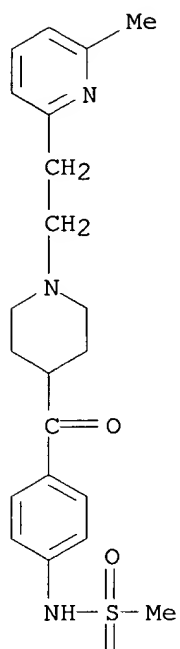


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RN 113558-89-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

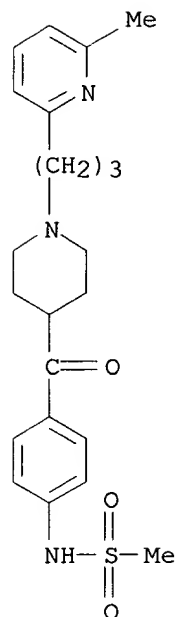
PAGE 1-A



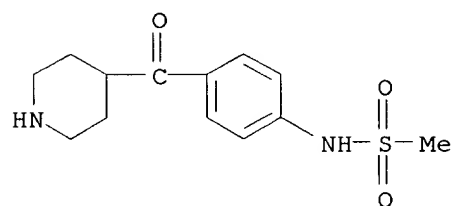
PAGE 2-A



RN 124536-77-2 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(6-methyl-2-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

IT **113559-02-7P**RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction with alkylpyridine derivs.)

RN 113559-02-7 HCAPLUS

CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

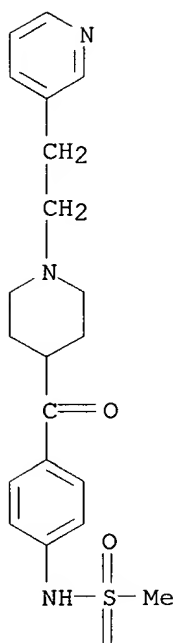
● HCl

IT **113559-11-8P 113559-12-9P 113559-13-0P**RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 113559-11-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(3-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

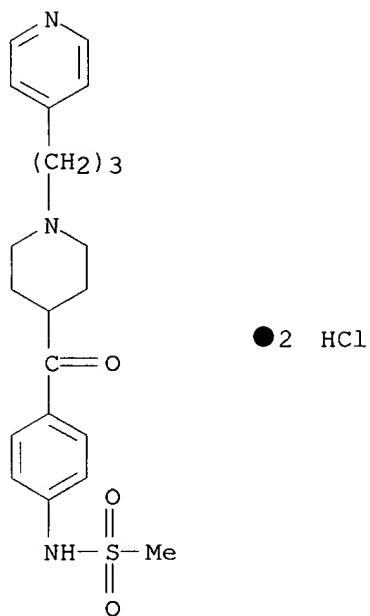


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● 2 HCl

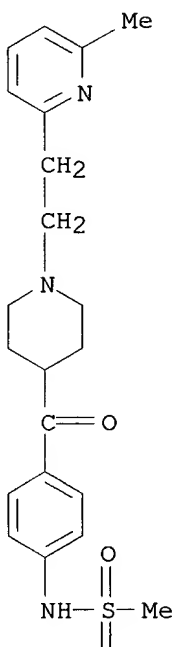
RN 113559-12-9 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-13-0 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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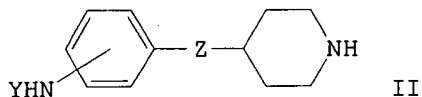
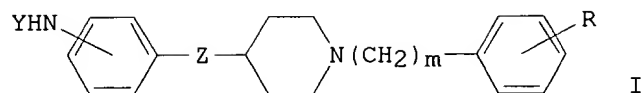
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●2 HCl

L14 ANSWER 180 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1990:7382 HCAPLUS
 DOCUMENT NUMBER: 112:7382
 TITLE: Preparation of N-phenylalkylpiperidines as serotonin
 5HT2 antagonists
 INVENTOR(S): Carr, Albert A.; Dage, Richard C.; Koerner, John E.;
 Li, Tung; Miller, Francis P.
 PATENT ASSIGNEE(S): Merrell Dow Pharmaceuticals, Inc., USA
 SOURCE: Eur. Pat. Appl., 33 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| EP 320983 | A2 | 19890621 | EP 1988-121138 | 19881216 |
| EP 320983 | A3 | 19901010 | | |
| EP 320983 | B1 | 19950628 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| US 5093341 | A | 19920303 | US 1988-237600 | 19880826 |
| ZA 8809281 | A | 19890927 | ZA 1988-9281 | 19881212 |
| DK 8806980 | A | 19890618 | DK 1988-6980 | 19881215 |
| DK 173764 | B1 | 20010917 | | |
| FI 8805827 | A | 19890618 | FI 1988-5827 | 19881216 |
| NO 8805607 | A | 19890619 | NO 1988-5607 | 19881216 |
| NO 174503 | B | 19940207 | | |
| NO 174503 | C | 19940518 | | |
| AU 8827000 | A1 | 19890622 | AU 1988-27000 | 19881216 |
| AU 612743 | B2 | 19910718 | | |
| CN 1033805 | A | 19890712 | CN 1988-108620 | 19881216 |
| JP 01197469 | A2 | 19890809 | JP 1988-316632 | 19881216 |
| JP 2835731 | B2 | 19981214 | | |
| HU 50121 | A2 | 19891228 | HU 1988-6478 | 19881216 |
| HU 202493 | B | 19910328 | | |
| HU 52051 | A2 | 19900628 | HU 1989-4865 | 19881216 |
| HU 203534 | B | 19910828 | | |
| CA 1322007 | A1 | 19930907 | CA 1988-586190 | 19881216 |
| ES 2076155 | T3 | 19951101 | ES 1988-121138 | 19881216 |
| US 5166211 | A | 19921124 | US 1991-797643 | 19911216 |
| US 5286866 | A | 19940215 | US 1992-837462 | 19920214 |
| PRIORITY APPLN. INFO.: | | | US 1987-134406 | A 19871217 |
| | | | US 1988-237600 | A 19880826 |
| | | | US 1991-797643 | A3 19911216 |
| OTHER SOURCE(S): MARPAT 112:7382 | | | | |
| GI | | | | |

Searched by Thom Larson, STIC, 308-7309



AB Title compds. I [Y = H, Me(CH₂)_nCO (n = 0-3), Me(CH₂)_nSO₂; Z = CO, CHOH, C:NOA (A = H, C1-4 alkyl); R = H, halo, alkyl, alkoxy; divalent R = 3,4-O(CH₂)₁₀ (l = 1,2); m = 1-5; when Z = CO, CHOH, Y = Me(CH₂)_nSO₂], useful as serotonin 5HT₂ antagonists (no data), are prepd. via piperidines II (definition is same as I). I are useful for treating anxiety, variant angina, anorexia nervosa, fibromyalgia, extrapyramidal symptoms, etc. (no data). Treatment of PhNHAc with 4-(chlorocarbonyl)piperidine HCl in the presence of AlCl₃ gave II (YNH = 4-AcNH; Z = CO), which in DMF was treated with Ph(CH₂)₂Br in the presence of K₂CO₃ to afford I (YNH = AcNH; Z = CO; m = 2; R = H).

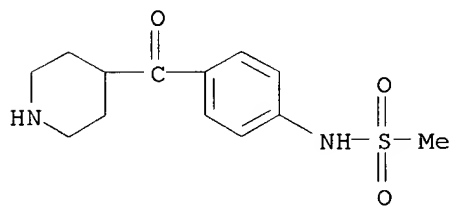
IT **113558-82-0P 113559-02-7P 124035-23-0P**

124894-08-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of serotonin antagonists)

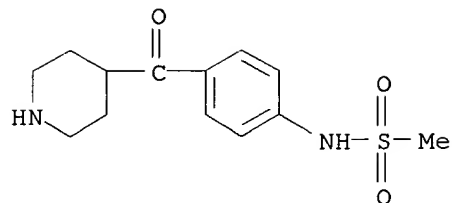
RN 113558-82-0 HCAPLUS

CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]- (9CI) (CA INDEX NAME)



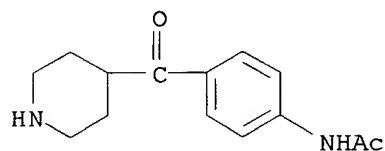
RN 113559-02-7 HCAPLUS

CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

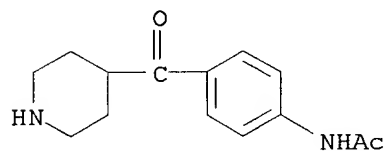


● HCl

RN 124035-23-0 HCAPLUS
CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]- (9CI) (CA INDEX NAME)

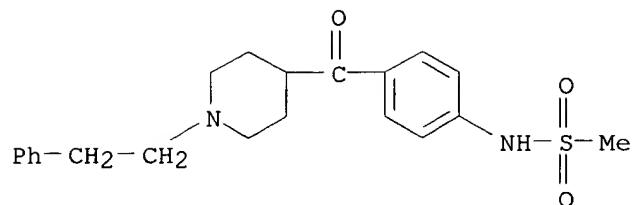


RN 124894-08-2 HCAPLUS
CN Acetamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride (9CI)
(CA INDEX NAME)



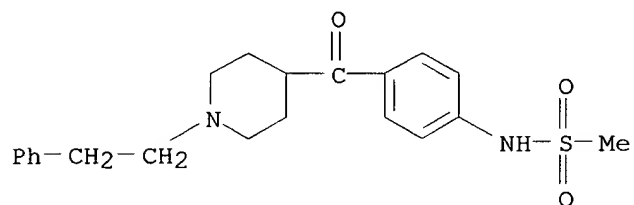
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IT 113558-86-4P 113559-41-4P 113559-48-1P
124035-09-2P 124035-10-5P 124035-13-8P
124035-14-9P 124035-17-2P 124035-18-3P
124035-21-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as serotonin antagonist)
RN 113558-86-4 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113559-41-4 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

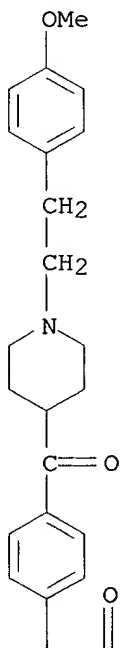


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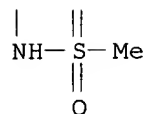
RN 113559-48-1 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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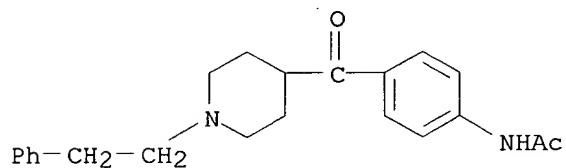


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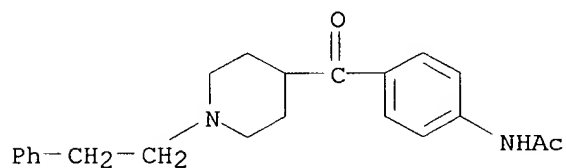
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RN 124035-09-2 HCAPLUS

CN Acetamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]- (9CI)
(CA INDEX NAME)

RN 124035-10-5 HCAPLUS

CN Acetamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

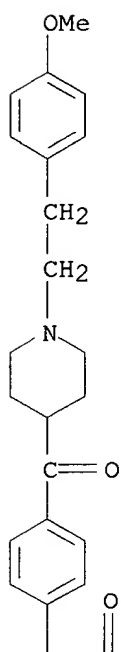


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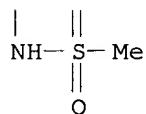
RN 124035-13-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

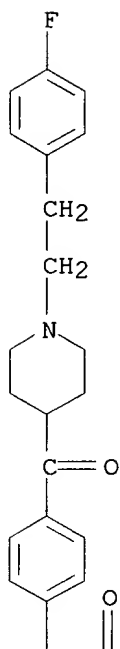


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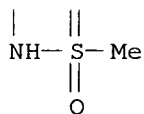


RN 124035-14-9 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

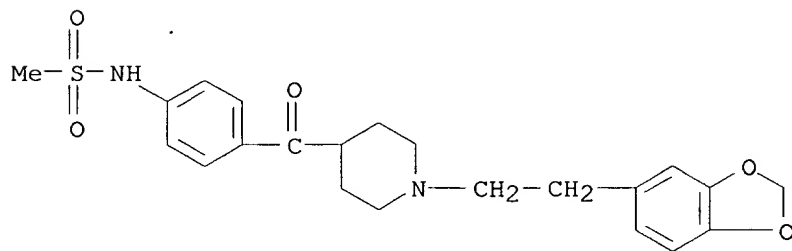


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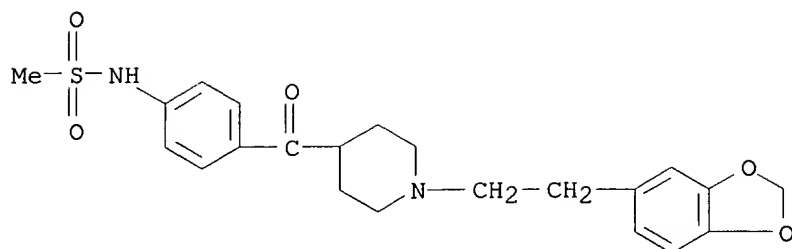
RN 124035-17-2 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(1,3-benzodioxol-5-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



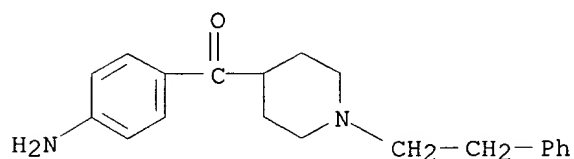
RN 124035-18-3 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(1,3-benzodioxol-5-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 124035-21-8 HCAPLUS
 CN Methanone, (4-aminophenyl) [1-(2-phenylethyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

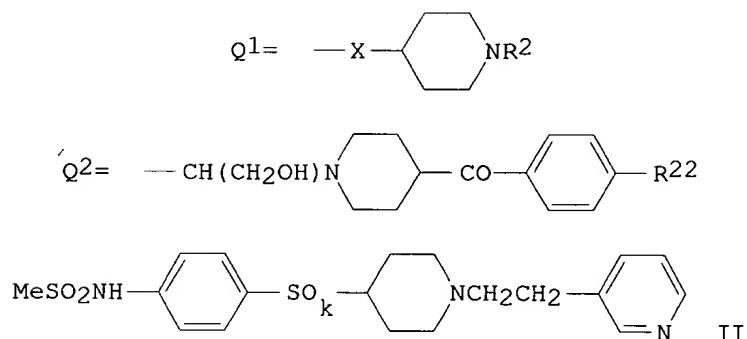


L14 ANSWER 181 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1989:533993 HCAPLUS
 DOCUMENT NUMBER: 111:133993
 TITLE: Preparation of piperidines as antiarrhythmic agents
 INVENTOR(S): Oinuma, Hitoshi; Yamanaka, Motosuke; Miyake, Kazutoshi; Hoshiko, Tomonori; Minami, Norio; Shoji, Tadao; Daiku, Yoshiharu; Sawada, Kohei; Nomoto, Kenichi
 PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
 SOURCE: Eur. Pat. Appl., 56 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 304888 | A1 | 19890301 | EP 1988-113786 | 19880824 |
| EP 304888 | B1 | 19921111 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| JP 01052756 | A2 | 19890228 | JP 1987-209726 | 19870824 |
| JP 2637989 | B2 | 19970806 | | |
| JP 01052752 | A2 | 19890228 | JP 1987-209727 | 19870824 |
| JP 08019083 | B4 | 19960228 | | |
| JP 01052717 | A2 | 19890228 | JP 1987-209728 | 19870824 |
| JP 2584454 | B2 | 19970226 | | |
| US 4977165 | A | 19901211 | US 1988-234468 | 19880819 |
| NO 8803750 | A | 19890227 | NO 1988-3750 | 19880822 |

Searched by Thom Larson, STIC, 308-7309

| | | | | |
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| DK 8804704 | A | 19890225 | DK 1988-4704 | 19880823 |
| HU 48587 | A2 | 19890628 | HU 1988-4430 | 19880823 |
| HU 207043 | B | 19930301 | | |
| CA 1263658 | A1 | 19891205 | CA 1988-575436 | 19880823 |
| AT 82263 | E | 19921115 | AT 1988-113786 | 19880824 |
| ES 2045044 | T3 | 19940116 | ES 1988-113786 | 19880824 |
| US 5082850 | A | 19920121 | US 1990-571313 | 19900822 |
| US 5162347 | A | 19921110 | US 1991-703208 | 19910520 |
| US 5246946 | A | 19930921 | US 1992-930727 | 19920814 |
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| | | | EP 1988-113786 | 19880824 |
| | | | US 1990-571313 | 19900822 |
| | | | US 1991-703208 | 19910520 |
| OTHER SOURCE(S): | | | MARPAT 111:133993 | |
| GI | | | | |



AB R1SO2NHC6H4W-4 [I; R1 = alkyl; W = X1(CH2)pNR12Y1, Q1, Q2; R2 = H, (CH2)nY; R12 = H, alkyl; R22 = H, OH, halo, alkyl, alkoxy; X = S, SO, SO2; X1 = CO, CH(OH); Y = aryl, (un)substituted pyridyl; Y1 = (CH2)mA; A = (un)substituted aryl, pyridyl; NR12Y1 = (un)substituted heterocyclyl; m = 1, 2; n = 1-5; p = 1-4] were prepd. N-Benzoyl-4-bromopiperidine (prepn. given) was stirred 1.5 h at 90.degree. with RSH [R = 4-(MeSO2NH)C6H4] (prepn. given) in DMF contg. K2CO3 and KI to give, after hydrolysis, RQ1.HCl (R as above, R2 = Bz, X = S) which was stirred 40 min at 85.degree. with NaHCO3, followed by addn. of KI and 2-(3-pyridyl)ethyl chloride-HCl and stirring 1.5 h at 85.degree., to give (phenylthio)(pyridylethyl)piperidine II (k = 0). The latter was stirred 1 h with NaIO4 in MeOH contg. aq. HCl to give II (k = 1) which gave 40% prolongation of action potential duration in isolated guinea pig myocardium at 10-5 M with no Vmax inhibition.

IT **122374-69-0P**

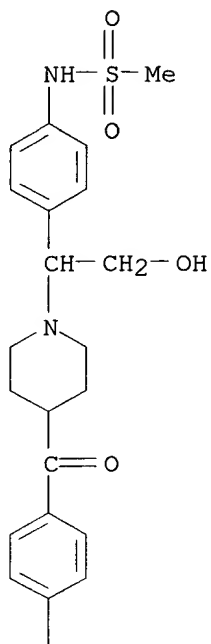
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(prepn. of, as antiarrhythmic agent)

RN 122374-69-0 HCAPLUS

CN Methanesulfonamide, N-[4-[2-hydroxy-1-[4-(4-hydroxybenzoyl)-1-

piperidiny]ethyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L14 ANSWER 182 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1989:423390 HCAPLUS
 DOCUMENT NUMBER: 111:23390
 TITLE: Benzopyran derivatives as antiarrhythmics, their preparation and formulations containing them
 INVENTOR(S): Hardy, Jean Claude; Renault, Christian
 PATENT ASSIGNEE(S): Rhone-Poulenc Sante, Fr.
 SOURCE: Eur. Pat. Appl., 31 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| EP 300908 | A1 | 19890125 | EP 1988-401890 | 19880721 |
| EP 300908 | B1 | 19920318 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
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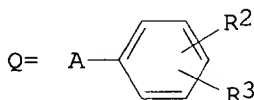
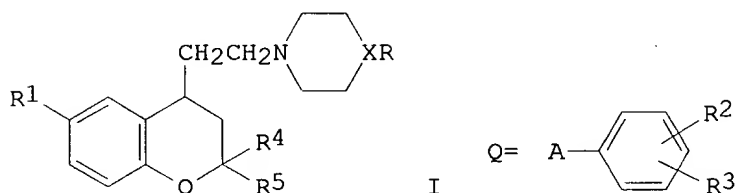
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| FR 2618437 | B1 | 19891117 | | |
| JP 01040476 | A2 | 19890210 | JP 1988-182768 | 19880721 |
| AT 73791 | E | 19920415 | AT 1988-401890 | 19880721 |
| DK 8804113 | A | 19890124 | DK 1988-4113 | 19880722 |
| FI 8803486 | A | 19890124 | FI 1988-3486 | 19880722 |
| NO 8803279 | A | 19890124 | NO 1988-3279 | 19880722 |
| AU 8819713 | A1 | 19890127 | AU 1988-19713 | 19880722 |
| AU 606184 | B2 | 19910131 | | |
| ZA 8805374 | A | 19890329 | ZA 1988-5374 | 19880722 |
| HU 54145 | A2 | 19910128 | HU 1988-3880 | 19880722 |
| US 4977166 | A | 19901211 | US 1989-327093 | 19890322 |

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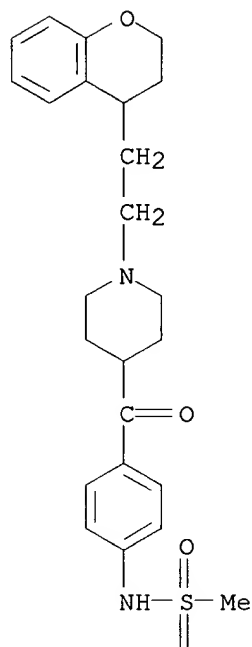
OTHER SOURCE(S): CASREACT 111:23390

GI



- AB The title compds. I (R1 = H, halo, OH, NO2, NH2, acylamino, etc.; X = N, CH; R = Q; A = bond, methylene; when X = N, A may be carbonyl; R2, R3 = H, halo, OH, alkyl, NO2, cyano, etc.; or R2R3 = methylenedioxy, ethylenedioxy; or R = pyridyl, 2H-benzimidazolonyl when X = CH; R4, R5 = H, alkyl), useful as antiarrhythmics, were prepd. A mixt. of 4-(2-bromoethyl)-3,4-dihydro-2H-benzopyran, 4-(3,4-dimethoxyphenyl)piperidine, K2CO3, and KI in 2-butanone was refluxed for 3 h to give, after workup and acidification, 1-[2-(3,4-dihydro-2H-1-benzopyran-4-yl)ethyl]-4-(3,4-dimethoxyphenyl)piperidine-HCl (II). In an in vitro test using the guinea pig papillary muscle, I (amt. unspecified) increased the duration of the initial action potential by 5 to >50%. Tablets contg. II 136.7, lactose 50 mg, and excipient q.s. to 250 mg were prepd.
- IT **121278-24-8P**
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of, as antiarrhythmic)
- RN 121278-24-8 HCAPLUS
- CN Methanesulfonamide, N-[4-[[1-[2-(3,4-dihydro-2H-1-benzopyran-4-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



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● HCl

L14 ANSWER 183 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1988:167305 HCAPLUS
 DOCUMENT NUMBER: 108:167305
 TITLE: Preparation of [(sulfonylamino)benzoyl]piperidines as
 antiarrhythmic agents
 INVENTOR(S): Oinuma, Hitoshi; Yamanaka, Motosuke; Miyake,
 Kazutoshi; Hoshiko, Tomonori; Minami, Norio; Shoji,
 Tadao; Daiku, Yoshiharu; Sawada, Kohei; Nomoto,
 Kenichi
 PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
 SOURCE: Eur. Pat. Appl., 29 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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Searched by Thom Larson, STIC, 308-7309

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| EP 235752 | A2 | 19870909 | EP 1987-102743 | 19870226 |
| EP 235752 | A3 | 19900725 | | |
| EP 235752 | B1 | 19931118 | | |
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| US 4876262 | A | 19891024 | US 1987-16035 | 19870218 |
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| NO 8700747 | A | 19870827 | NO 1987-747 | 19870224 |
| NO 170484 | B | 19920713 | | |
| NO 170484 | C | 19921021 | | |
| CN 87100928 | A | 19870909 | CN 1987-100928 | 19870225 |
| CN 1019973 | B | 19930303 | | |
| JP 62281858 | A2 | 19871207 | JP 1987-42368 | 19870225 |
| JP 07080841 | B4 | 19950830 | | |
| HU 46675 | A2 | 19881128 | HU 1987-730 | 19870225 |
| HU 199794 | B | 19900328 | | |
| CA 1317941 | A1 | 19930518 | CA 1987-530571 | 19870225 |
| AU 8769513 | A1 | 19870827 | AU 1987-69513 | 19870226 |
| AU 599632 | B2 | 19900726 | | |
| AT 97405 | E | 19931215 | AT 1987-102743 | 19870226 |
| ES 2059315 | T3 | 19941116 | ES 1987-102743 | 19870226 |
| US 4996215 | A | 19910226 | US 1989-408106 | 19890915 |
| US 5118689 | A | 19920602 | US 1990-594079 | 19901009 |
| US 5179095 | A | 19930112 | US 1991-798963 | 19911126 |
| JP 06293732 | A2 | 19941021 | JP 1993-310441 | 19931210 |
| JP 07076208 | B4 | 19950816 | | |
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| | | | US 1989-408106 | 19890915 |
| | | | US 1990-594079 | 19901009 |

OTHER SOURCE(S): CASREACT 108:167305

GI For diagram(s), see printed CA Issue.

AB The title compds. [I; R1 = alkyl, tolyl; R2 = H, OH, alkyl, alkoxy; R3 = H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl; X = CO, CH₂, CHOH; Y = R₃, CH₂CO₂R, Q, AB; A = alkylene, alkenylene, CH₂C(:CH₂), (CH₂)_kS, (CH₂)_pCO; B = cyano, NR₄R₅, naphthyl, (un)substituted Ph, heterocyclyl; R, R₄, R₅ = H, alkyl; g, h = 1-3; k = 2-5; l = 1, 2; p = 1-4] were prepd. as antiarrhythmic agents. 1-Acetylisonipecotoyl chloride and MeSO₂NHPh were added to CH₂Cl₂ contg. AlCl₃ and the mixt. refluxed 2 h to give [(sulfonylamino)benzoyl]piperidine II (Y = Ac) which was refluxed in 3N HCl for 3 h to give II.HCl (Y = H). At 0.1 mg/kg i.v. II.HCl (Y = CH₂CH₂Ph) caused a 51% prolongation of the QTc-interval in anesthetized dogs.

IT 113408-71-2P 113408-72-3P 113408-73-4P
 113558-75-1P 113558-76-2P 113558-77-3P
 113558-78-4P 113558-79-5P 113558-80-8P
 113558-81-9P 113558-82-0P 113558-83-1P
 113558-84-2P 113558-85-3P 113558-86-4P
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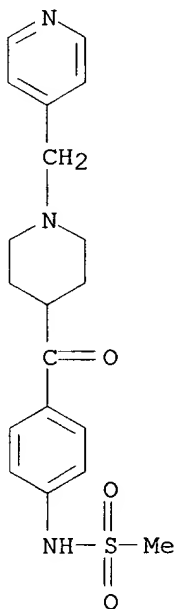
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RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antiarrhythmic agent)

RN 113408-71-2 HCAPLUS

CN Methanesulfonamide, N-[hydroxy-4-[[1-(4-pyridinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

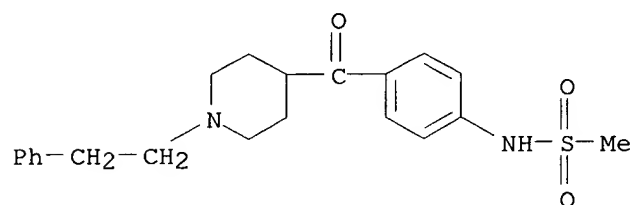


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D1-OH

● 2 HCl

RN 113408-72-3 HCAPLUS
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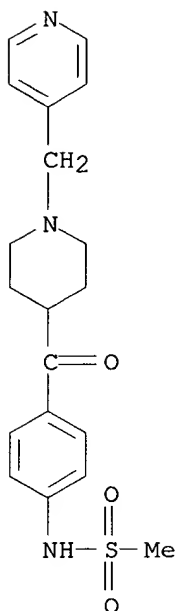


D1-OH

● HCl

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PAGE 1-A



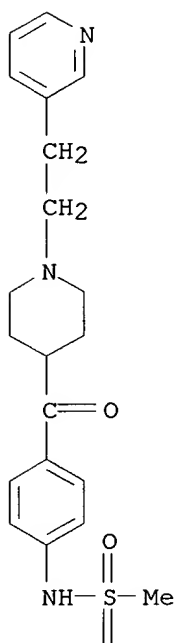
PAGE 2-A

D1-O-Me

● 2 HCl

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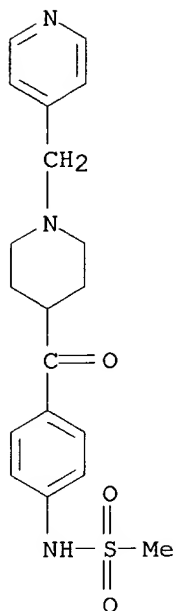
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PAGE 2-A

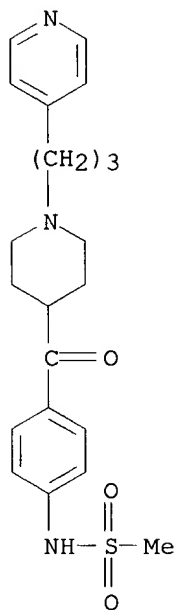


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RN 113558-77-3 HCAPLUS

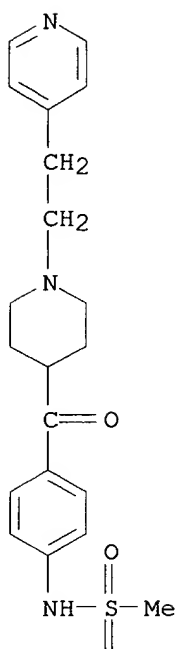
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RN 113558-78-4 HCAPLUS

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PAGE 1-A

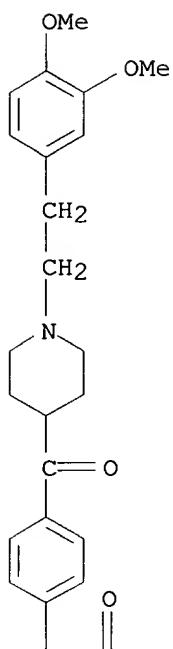


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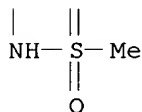


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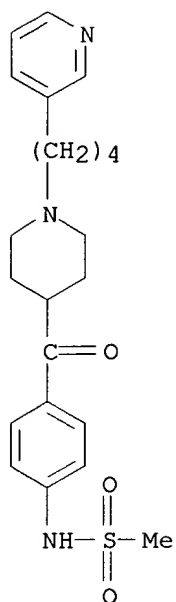
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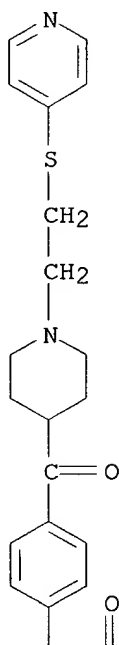
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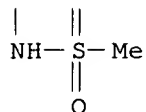
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PAGE 1-A



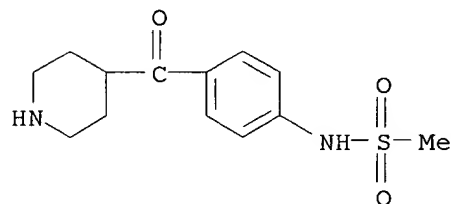
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PAGE 2-A



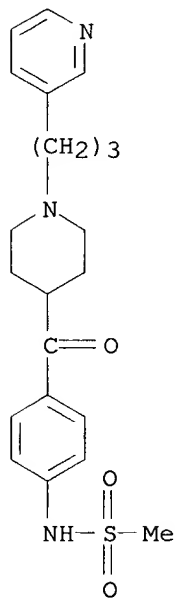
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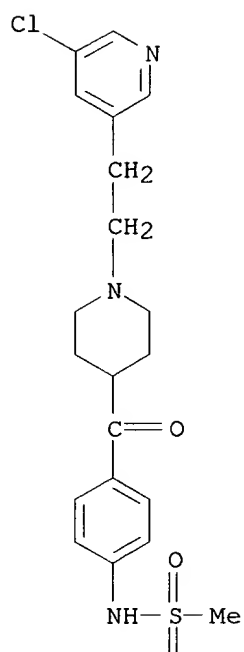
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RN 113558-84-2 HCAPLUS

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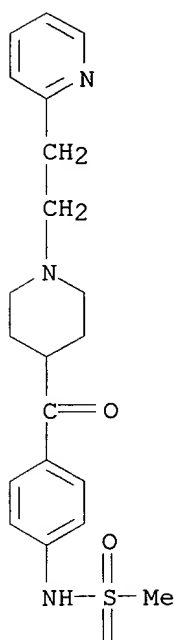


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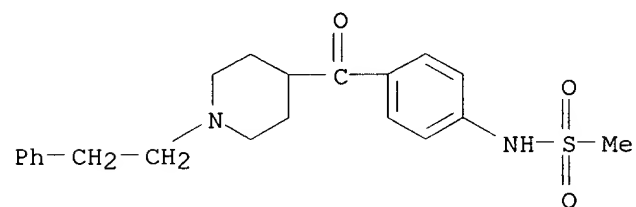
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PAGE 2-A

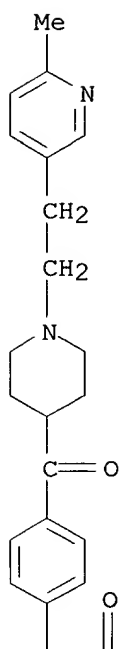


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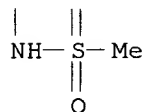


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PAGE 1-A

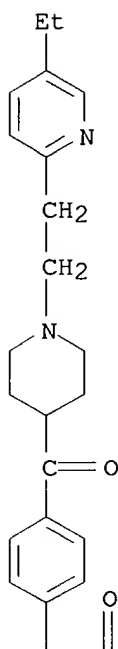


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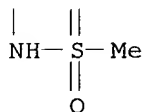


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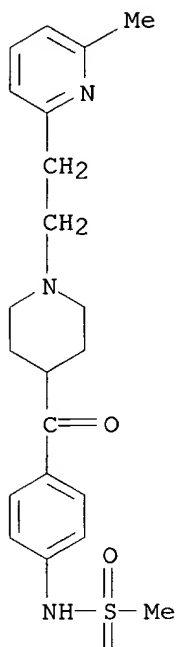


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RN 113558-89-7 HCAPLUS
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PAGE 1-A

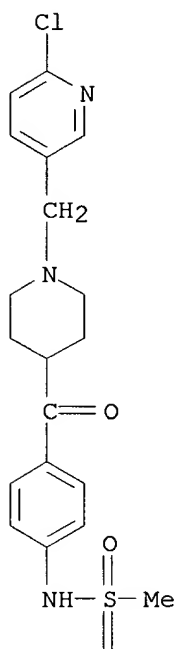


PAGE 2-A



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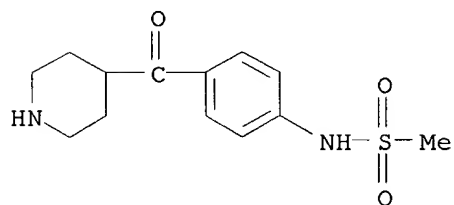
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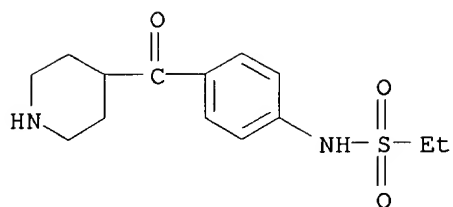
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CN Methanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

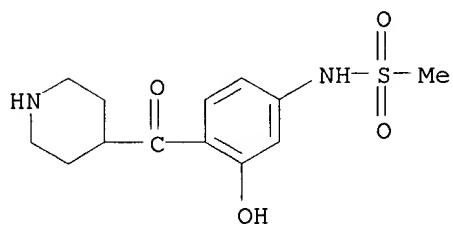
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CN Ethanesulfonamide, N-[4-(4-piperidinylcarbonyl)phenyl]-, monohydrochloride
(9CI) (CA INDEX NAME)



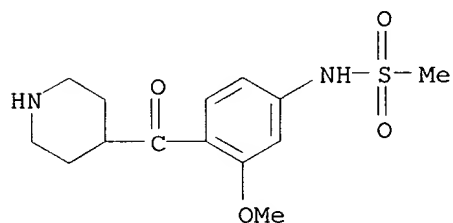
● HCl

RN 113559-04-9 HCAPLUS

CN Methanesulfonamide, N-[3-hydroxy-4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

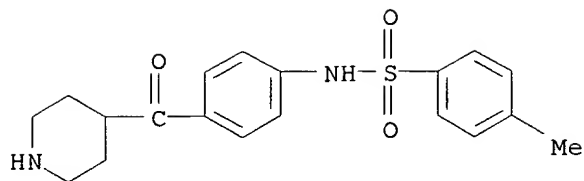
RN 113559-05-0 HCAPLUS

CN Methanesulfonamide, N-[3-methoxy-4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

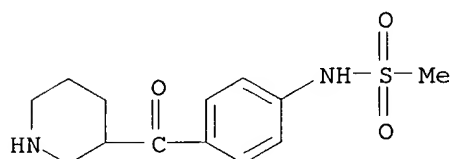
RN 113559-06-1 HCAPLUS

CN Benzenesulfonamide, 4-methyl-N-[4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)



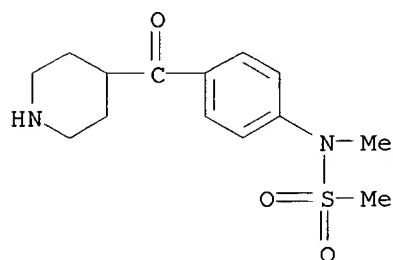
● HCl

RN 113559-08-3 HCAPLUS

CN Methanesulfonamide, N-[4-(3-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

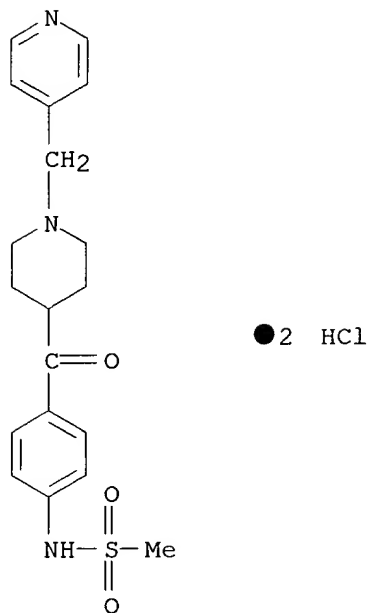
RN 113559-09-4 HCAPLUS

CN Methanesulfonamide, N-methyl-N-[4-(4-piperidinylcarbonyl)phenyl]-,
monohydrochloride (9CI) (CA INDEX NAME)

● HCl

RN 113559-10-7 HCAPLUS

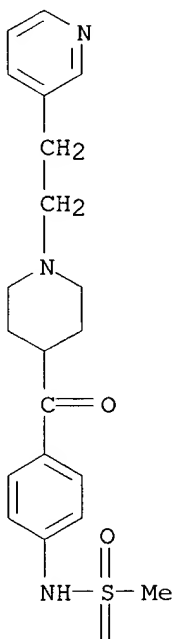
CN Methanesulfonamide, N-[4-[[1-(4-pyridinylmethyl)-4-piperidinyl]carbonyl]phenyl]-,
dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-11-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(3-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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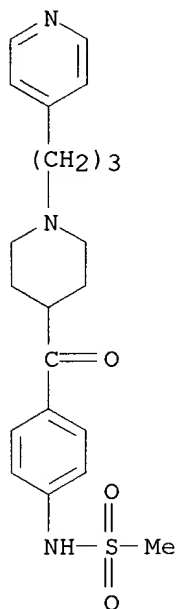


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●2 HCl

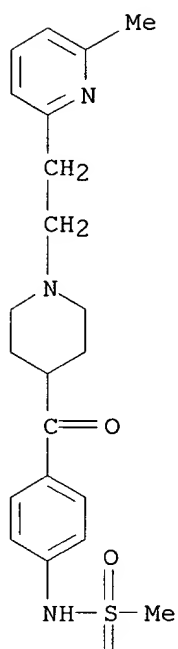
RN 113559-12-9 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 113559-13-0 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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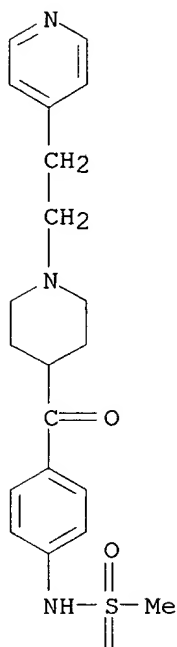
PAGE 2-A



● 2 HCl

RN 113559-14-1 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(4-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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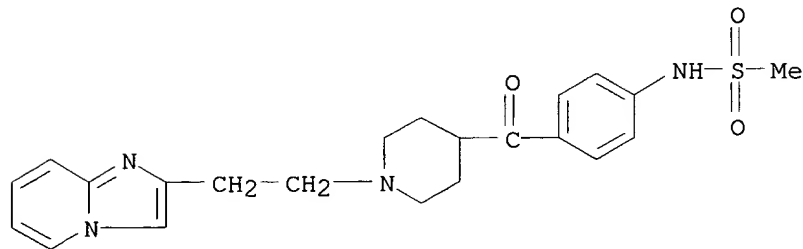


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● 2 HCl

RN 113559-15-2 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-imidazo[1,2-a]pyridin-2-ylethyl)-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



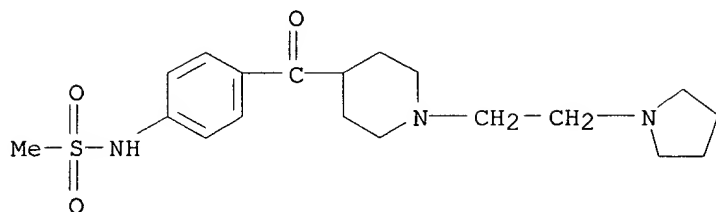
RN 113559-20-9 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(1-pyrrolidinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

Searched by Thom Larson, STIC, 308-7309

CM 1

CRN 113559-19-6

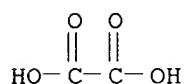
CMF C19 H29 N3 O3 S



CM 2

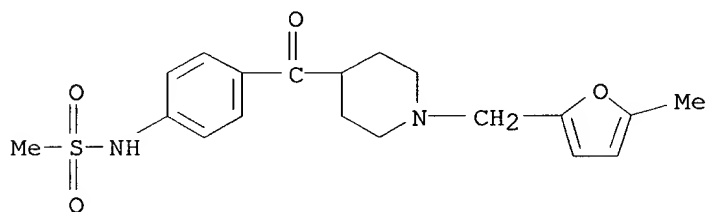
CRN 144-62-7

CMF C2 H2 O4



RN 113559-21-0 HCAPLUS

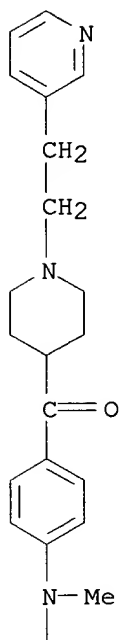
CN Methanesulfonamide, N-[4-[[1-[(5-methyl-2-furanyl)methyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



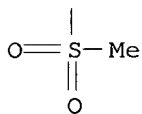
RN 113559-23-2 HCAPLUS

CN Methanesulfonamide, N-methyl-N-[4-[[1-[2-(3-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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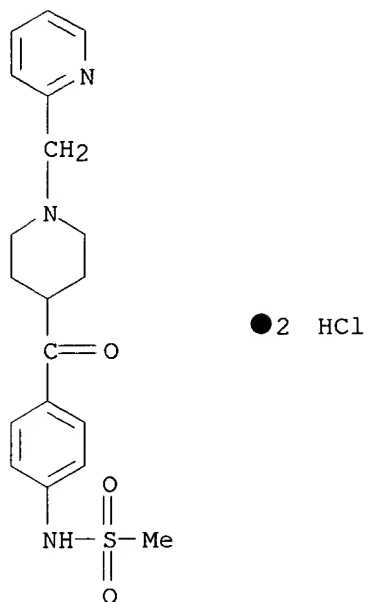


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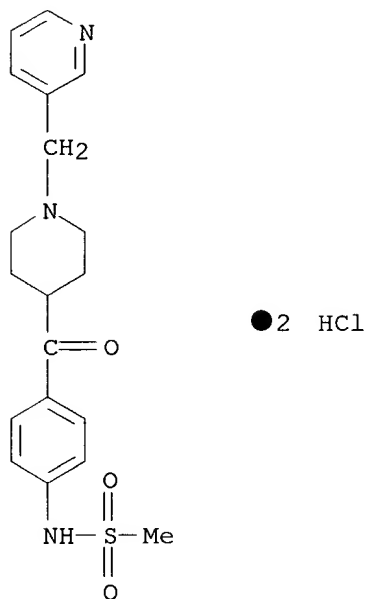
● 2 HCl

RN 113559-26-5 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-(2-pyridinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-27-6 HCAPLUS

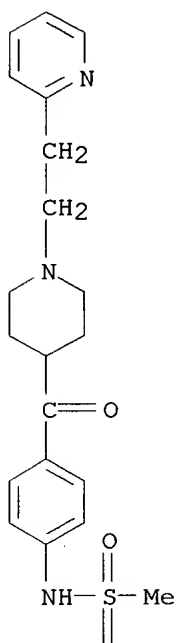
CN Methanesulfonamide, N-[4-[[1-(3-pyridinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-28-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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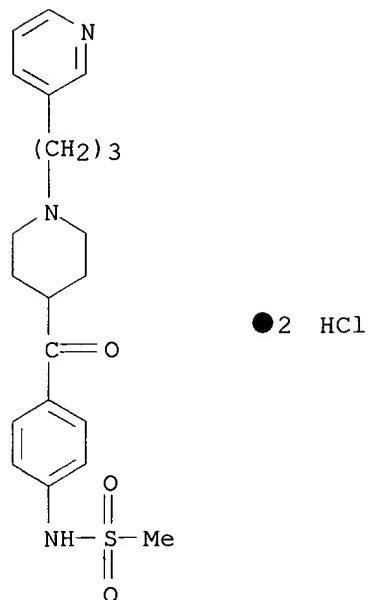


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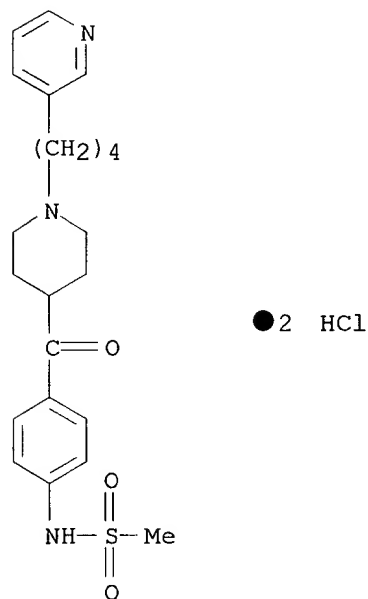
● 2 HCl

RN 113559-29-8 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(3-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



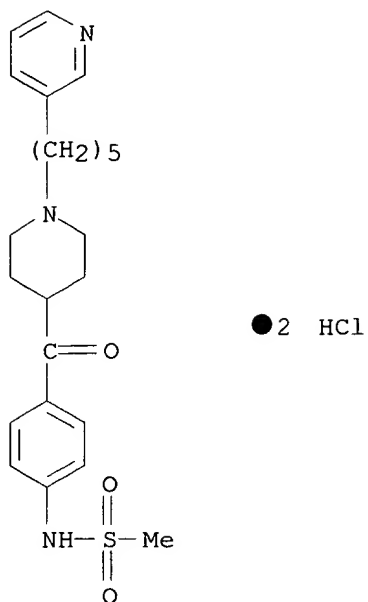
RN 113559-30-1 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[4-(3-pyridinyl)butyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-31-2 HCAPLUS

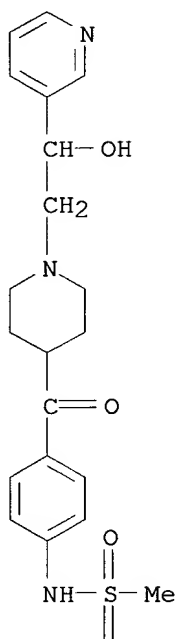
CN Methanesulfonamide, N-[4-[[1-[5-(3-pyridinyl)pentyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-32-3 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-hydroxy-2-(3-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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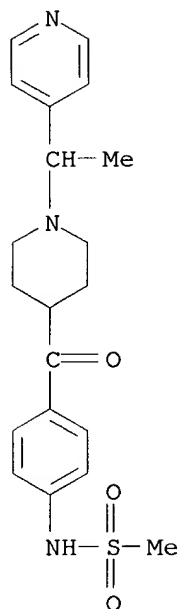


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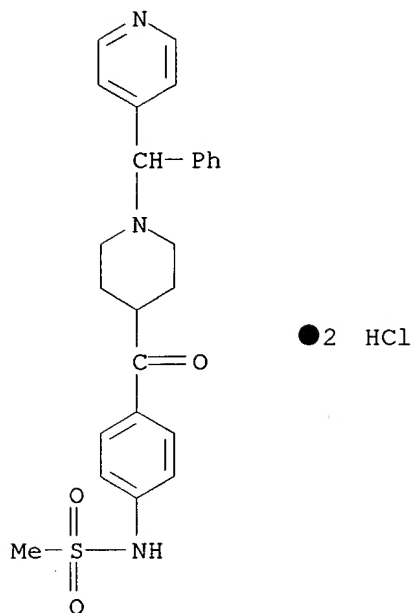
●2 HCl

RN 113559-34-5 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[1-(4-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



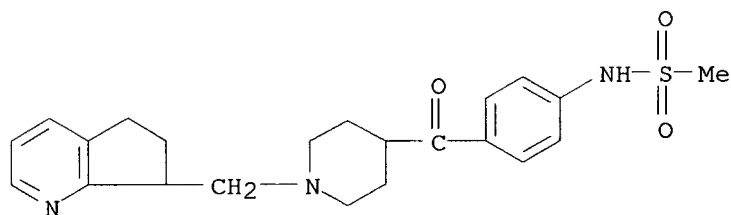
●2 HCl

RN 113559-35-6 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(phenyl-4-pyridinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-36-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[(6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl)methyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

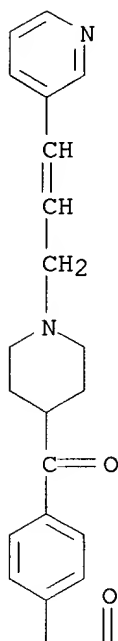


● 2 HCl

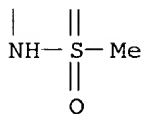
RN 113559-37-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[3-(3-pyridinyl)-2-propenyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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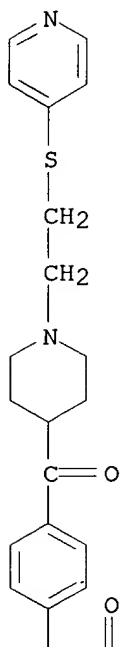
PAGE 2-A



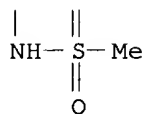
● 2 HCl

RN 113559-38-9 HCAPLUS
CN Methanesulfonamide, N-[4-[[[1-[2-(4-pyridinylthio)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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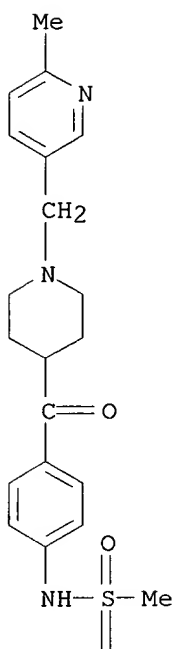
PAGE 2-A



● 2 HCl

RN 113559-39-0 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[(6-methyl-3-pyridinyl)methyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

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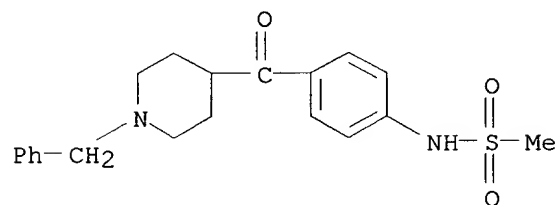


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RN 113559-40-3 HCAPLUS

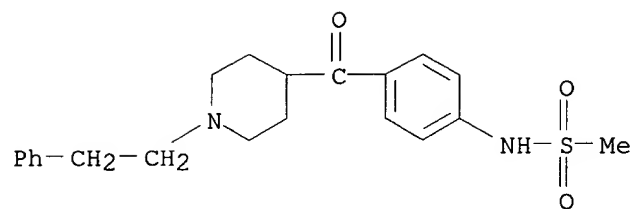
CN Methanesulfonamide, N-[4-[[1-(phenylmethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

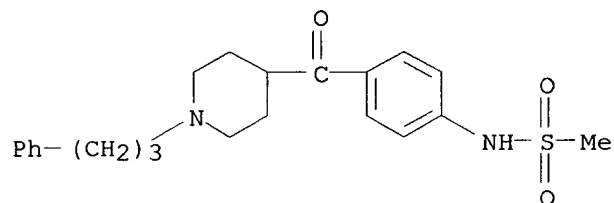
RN 113559-41-4 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

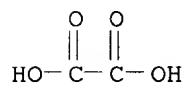


● HCl

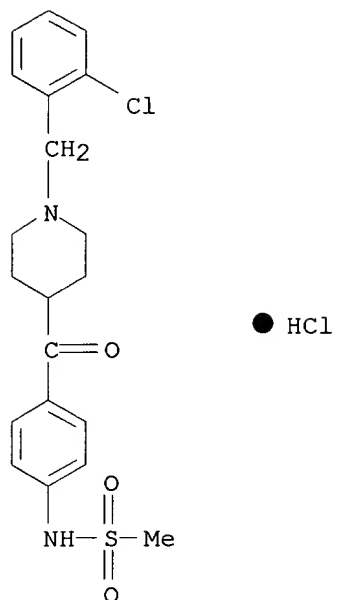
RN 113559-43-6 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(3-phenylpropyl)-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:1) (9CI) (CA INDEX NAME)
 CM 1
 CRN 113559-42-5
 CMF C22 H28 N2 O3 S



CM 2
 CRN 144-62-7
 CMF C2 H2 O4



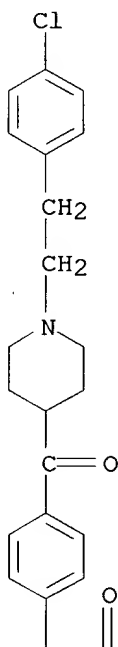
RN 113559-44-7 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[(2-chlorophenyl)methyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



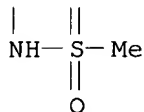
RN 113559-45-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-chlorophenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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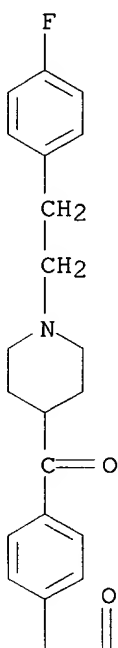
PAGE 2-A



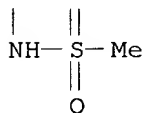
● HCl

RN 113559-46-9 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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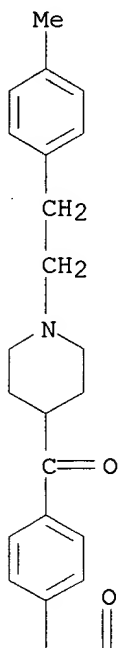


● HCl

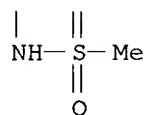
RN 113559-47-0 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-methylphenyl)ethyl]-4-

piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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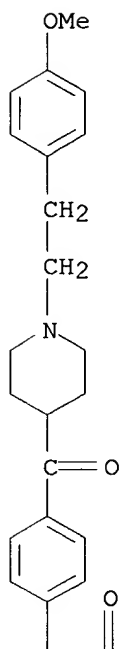
PAGE 2-A



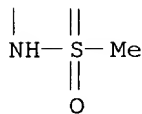
● HCl

RN 113559-48-1 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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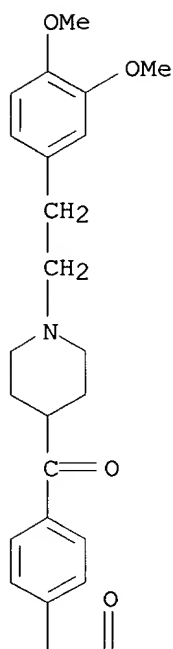
PAGE 2-A



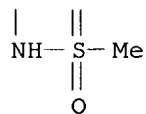
● HCl

RN 113559-49-2 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(3,4-dimethoxyphenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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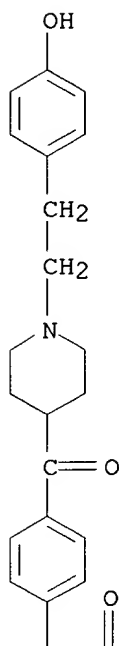
PAGE 2-A



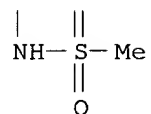
● HCl

RN 113559-50-5 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-hydroxyphenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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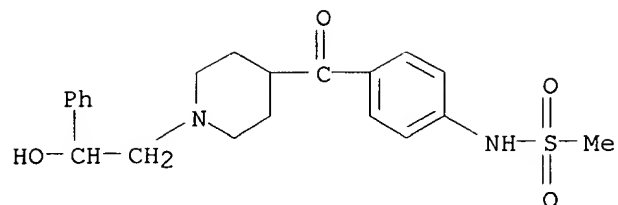


● HCl

RN 113559-52-7 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

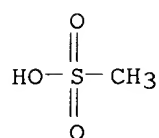
CRN 113559-51-6
 CMF C21 H26 N2 O4 S



CM 2

CRN 75-75-2

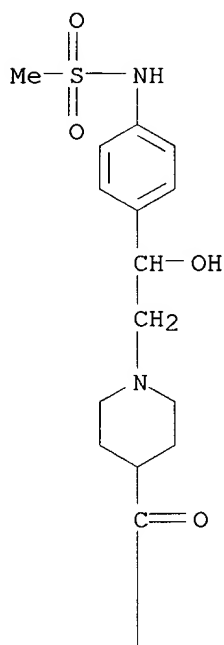
CMF C H4 O3 S



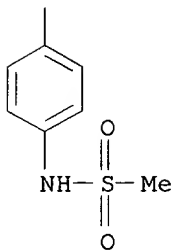
RN 113559-53-8 HCAPLUS

CN Methanesulfonamide, N-[4-[1-hydroxy-2-[4-[4-[(methanesulfonyl)amino]benzoyl]-1-piperidinyl]ethyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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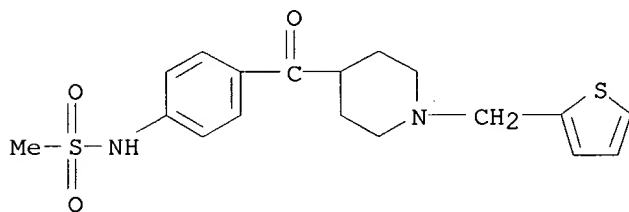


● HCl

RN 113559-56-1 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-thienylmethyl)-4-piperidinyl]carbonyl]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

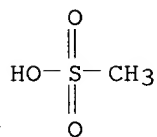
CM 1

CRN 113559-55-0
 CMF C18 H22 N2 O3 S2



CM 2

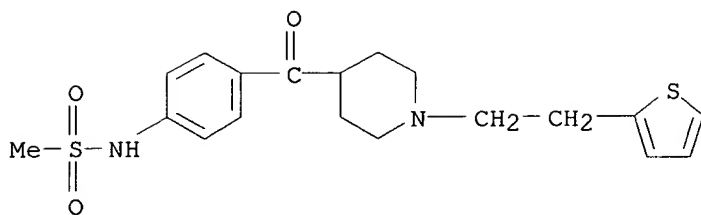
CRN 75-75-2
 CMF C H4 O3 S



RN 113559-58-3 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(2-thienyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

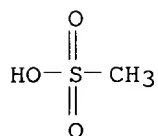
CRN 113559-57-2
 CMF C19 H24 N2 O3 S2



CM 2

CRN 75-75-2

CMF C H4 O3 S



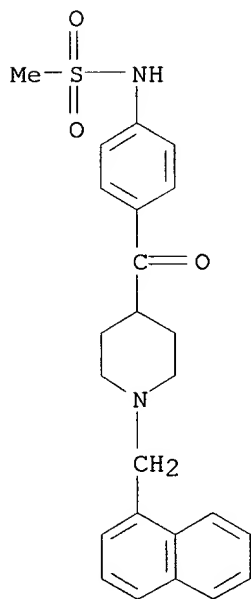
RN 113559-60-7 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(1-naphthalenylmethyl)-4-piperidinyl]carbonyl]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

CRN 113559-59-4

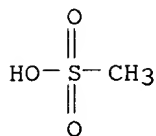
CMF C24 H26 N2 O3 S



CM 2

CRN 75-75-2

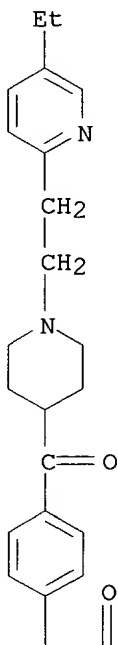
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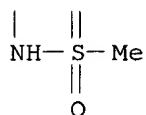
RN 113559-61-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(5-ethyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)

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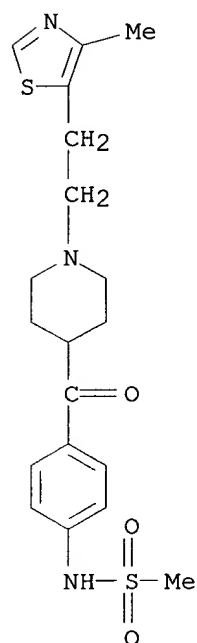


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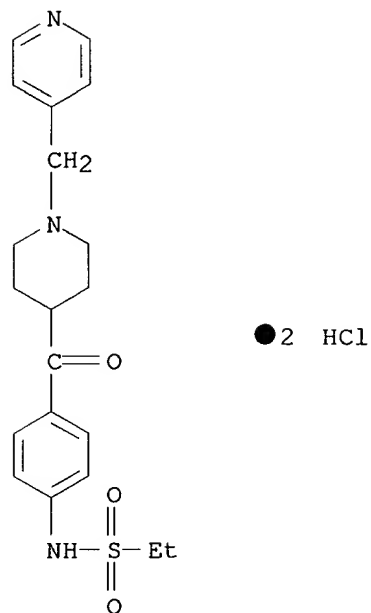
● 2 HCl

RN 113559-62-9 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(4-methyl-5-thiazolyl)ethyl]-4-piperidiny]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



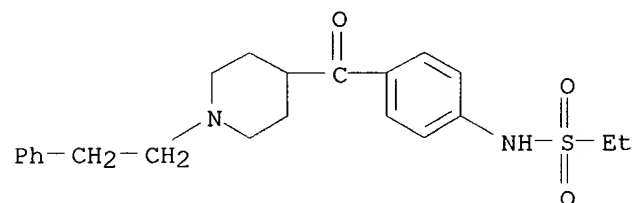
● 2 HCl

RN 113559-63-0 HCAPLUS
 CN Ethanesulfonamide, N-[4-[[1-(4-pyridinylmethyl)-4-piperidiny]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



RN 113559-64-1 HCAPLUS

CN Ethanesulfonamide, N-[4-[[1-(2-phenylethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

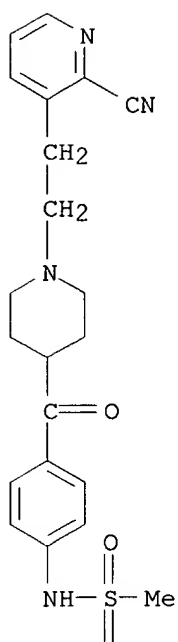


● HCl

RN 113559-66-3 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(2-cyano-3-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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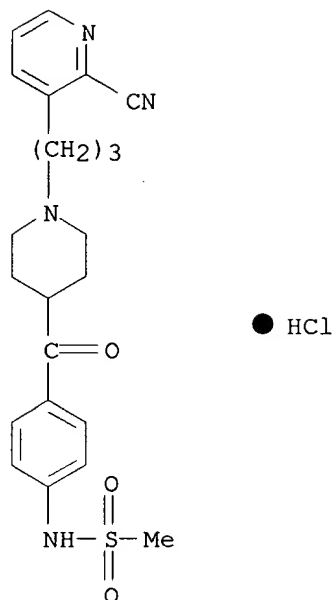


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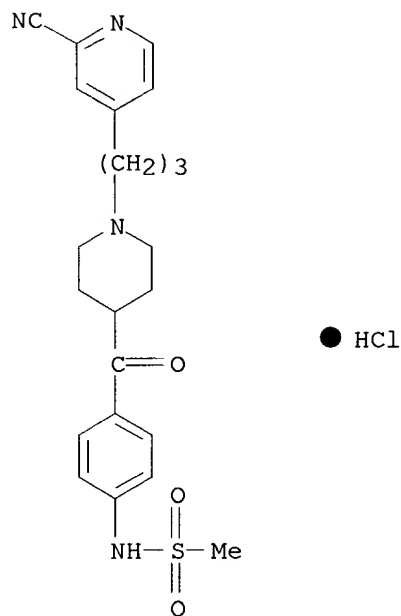
● HCl

RN 113559-67-4 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[3-(2-cyano-3-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



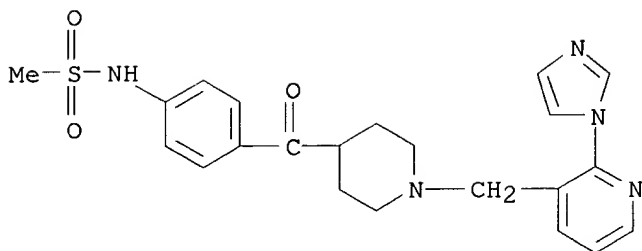
RN 113559-68-5 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[3-(2-cyano-4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



RN 113559-69-6 HCAPLUS

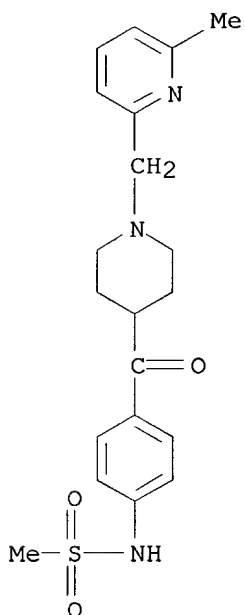
CN Methanesulfonamide, N-[4-[[1-[2-(1H-imidazol-1-yl)-3-pyridinyl]methyl]-4-piperidinyl]carbonyl]phenyl]-, trihydrochloride (9CI) (CA INDEX NAME)



● 3 HCl

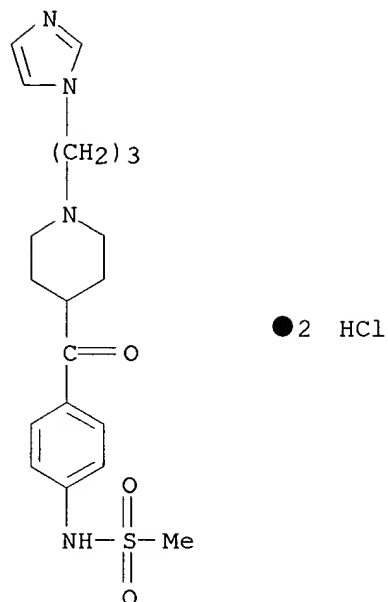
RN 113559-70-9 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[(6-methyl-2-pyridinyl)methyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113559-71-0 HCAPLUS

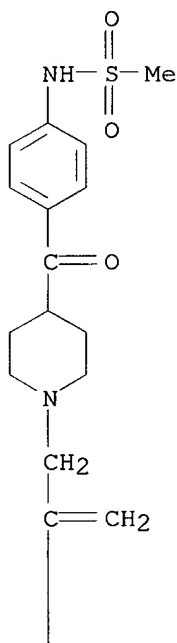
CN Methanesulfonamide, N-[4-[[1-[(3-(1H-imidazol-1-yl)propyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



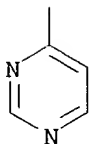
RN 113559-72-1 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(4-pyrimidinyl)-2-propenyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

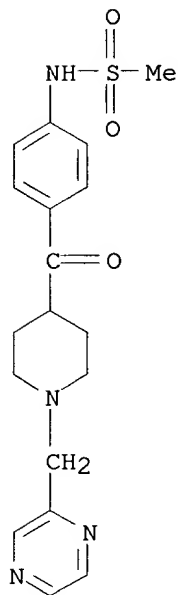
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RN 113559-73-2 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-(pyrazinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



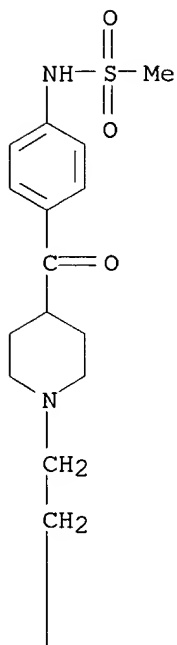
● 2 HCl

RN 113559-75-4 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-(2-pyrazinylethyl)-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (2:1) (9CI) (CA INDEX NAME)

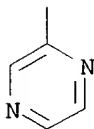
CM 1

CRN 113559-74-3
CMF C19 H24 N4 O3 S

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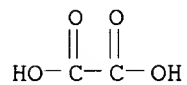
PAGE 2-A



CM 2

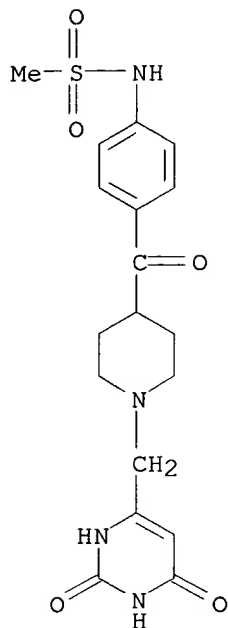
CRN 144-62-7

CMF C2 H2 O4



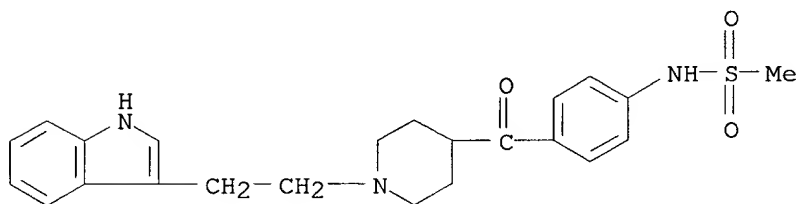
RN 113559-77-6 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)methyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113559-78-7 HCAPLUS

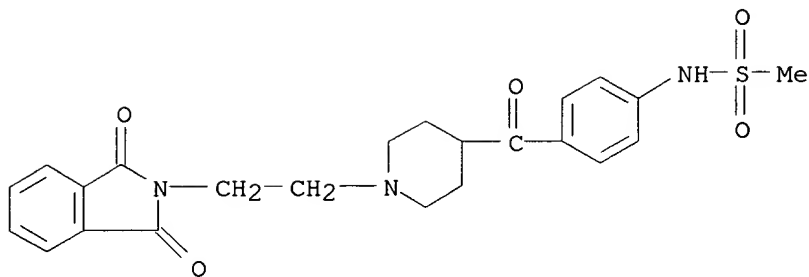
CN Methanesulfonamide, N-[4-[[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



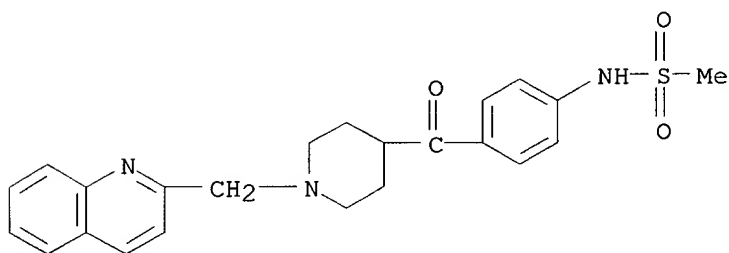
● HCl

RN 113559-79-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)

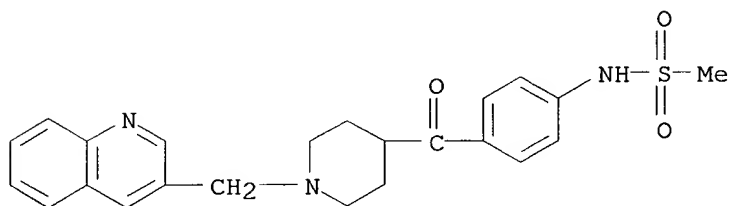


RN 113559-80-1 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-quinolinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



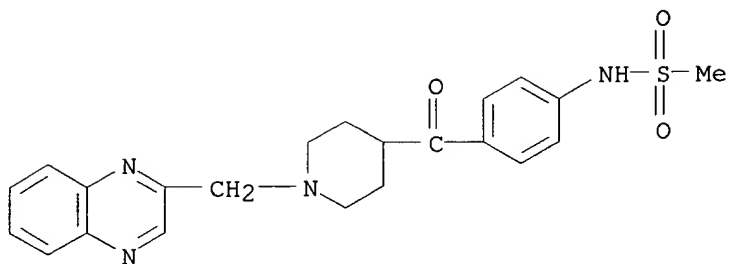
● 2 HCl

RN 113559-81-2 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(3-quinolinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

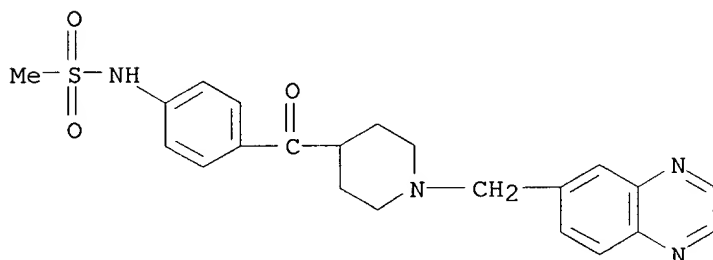
RN 113559-82-3 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-(2-quinoxalinylnmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

RN 113559-83-4 HCAPLUS

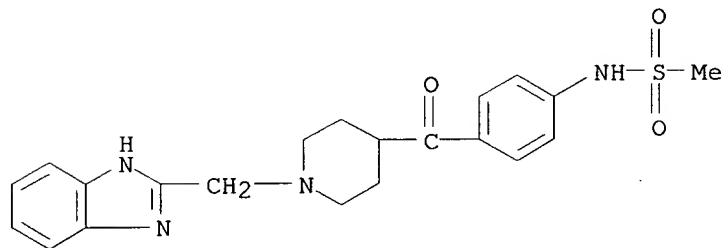
CN Methanesulfonamide, N-[4-[[1-(6-quinoxalinylmethyl)-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

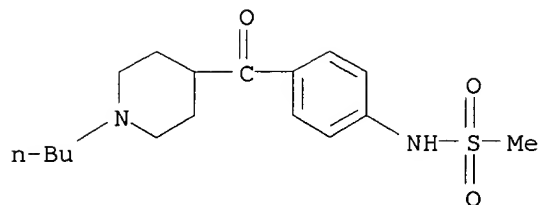
RN 113559-84-5 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(1H-benzimidazol-2-ylmethyl)-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113559-86-7 HCAPLUS

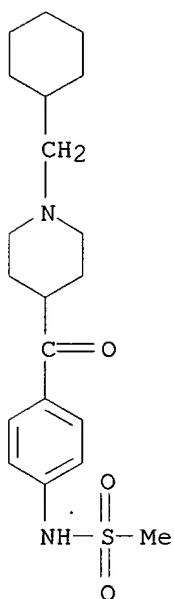
CN Methanesulfonamide, N-[4-[(1-butyl-4-piperidinyl)carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 113559-87-8 HCAPLUS

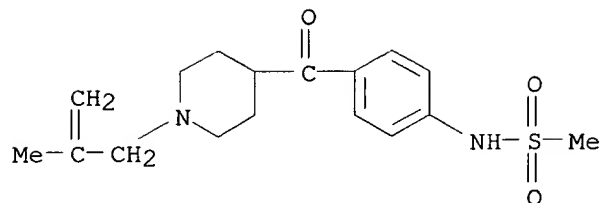
CN Methanesulfonamide, N-[4-[[1-(cyclohexylmethyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 113559-88-9 HCAPLUS

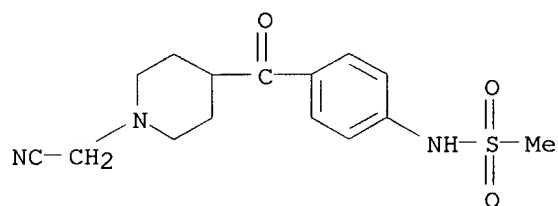
CN Methanesulfonamide, N-[4-[[1-(2-methyl-2-propenyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

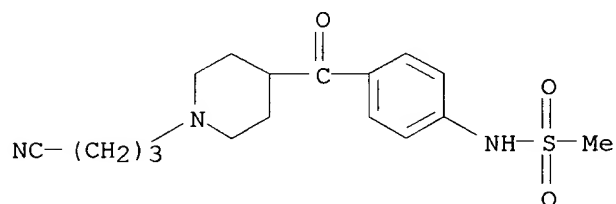
RN 113559-92-5 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(cyanomethyl)-4-piperidinyl]carbonyl]phenyl]-(9CI) (CA INDEX NAME)



RN 113559-93-6 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-(3-cyanopropyl)-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

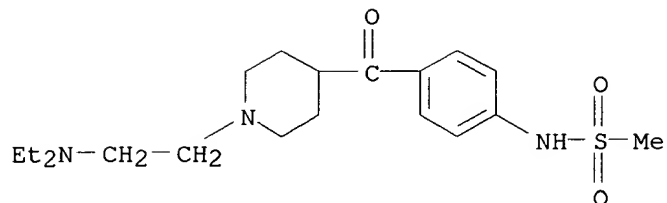
RN 113559-95-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(diethylamino)ethyl]-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 113559-94-7

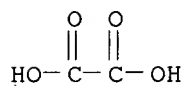
CMF C19 H31 N3 O3 S



CM 2

CRN 144-62-7

CMF C2 H2 O4



RN 113559-97-0 HCAPLUS

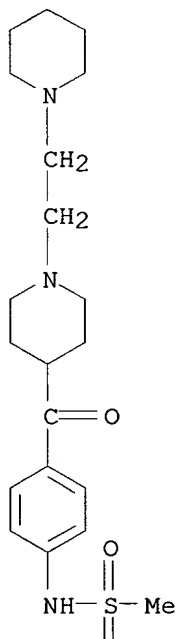
CN Methanesulfonamide, N-[4-[[1-[2-(1-piperidiny)ethyl]]-4-piperidiny]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 113559-96-9

CMF C20 H31 N3 O3 S

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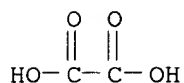
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CM 2

CRN 144-62-7

CMF C2 H2 O4



RN 113559-99-2 HCAPLUS

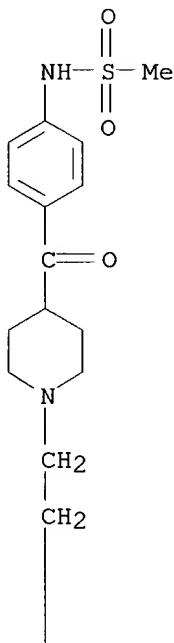
CN Methanesulfonamide, N-[4-[[1-[2-(4-morpholinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

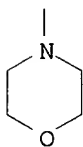
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CMF C19 H29 N3 O4 S

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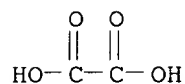
PAGE 2-A



CM 2

CRN 144-62-7

CMF C2 H2 O4



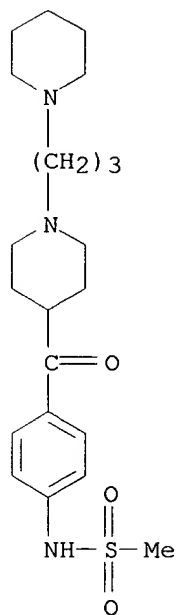
RN 113560-01-3 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[3-(1-piperidinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 113560-00-2

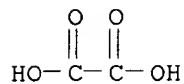
CMF C21 H33 N3 O3 S



CM 2

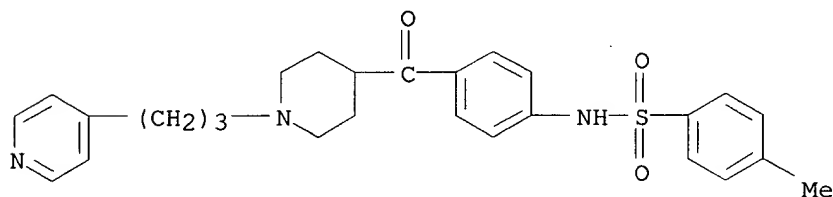
CRN 144-62-7

CMF C2 H2 O4



RN 113560-02-4 HCAPLUS

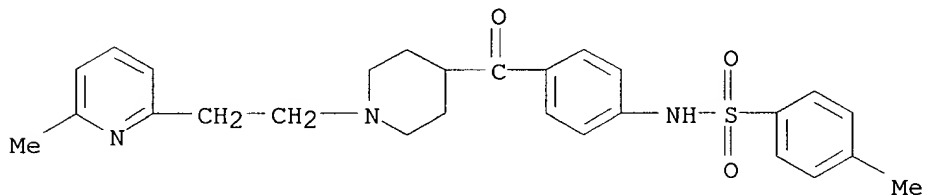
CN Benzenesulfonamide, 4-methyl-N-[4-[[1-[3-(4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

RN 113560-03-5 HCAPLUS

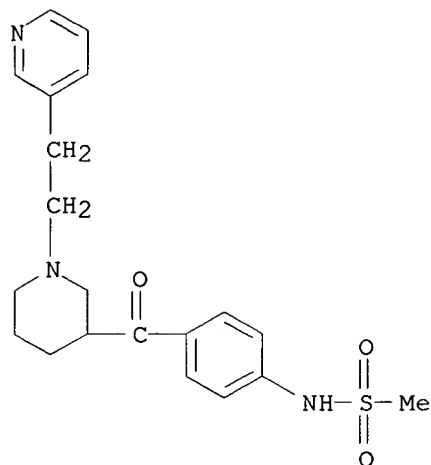
CN Benzenesulfonamide, 4-methyl-N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



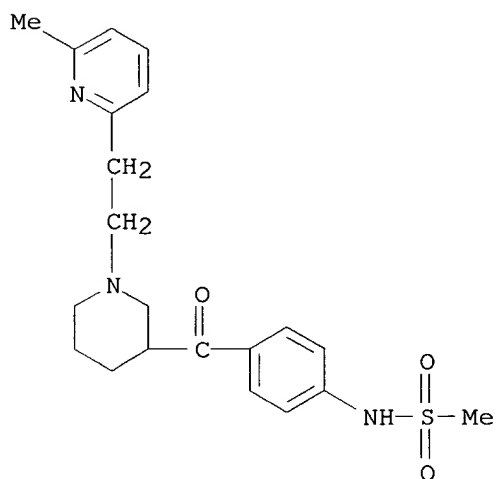
● 2 HCl

RN 113560-04-6 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(3-pyridinyl)ethyl]-3-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113560-05-7 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-3-piperidinyl]carbonyl]phenyl]-, dihydrochloride (9CI) (CA INDEX NAME)



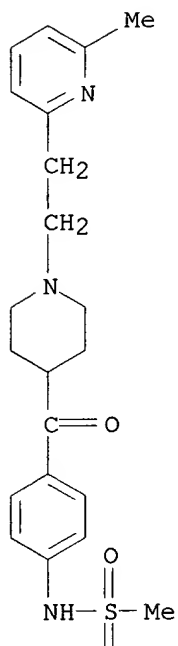
●2 HCl

RN 113560-06-8 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(6-methyl-2-pyridinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, ethanedioate (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 113558-89-7
 CMF C21 H27 N3 O3 S

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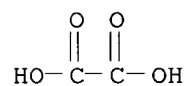


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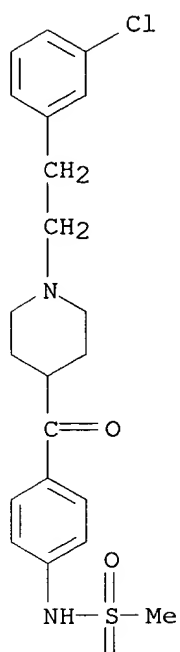
CM 2

CRN 144-62-7
 CMF C2 H2 O4



RN 113560-11-5 HCAPLUS
 CN Methanesulfonamide, N-[4-[[1-[2-(3-chlorophenyl)ethyl]-4-piperidinyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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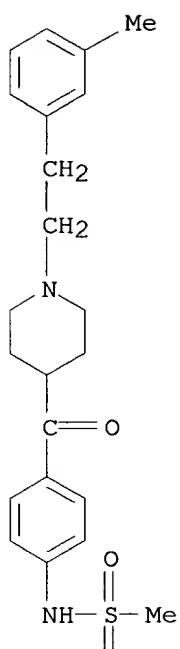
PAGE 2-A



● HCl

RN 113560-12-6 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[2-(3-methylphenyl)ethyl]-4-piperidyl]carbonyl]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)

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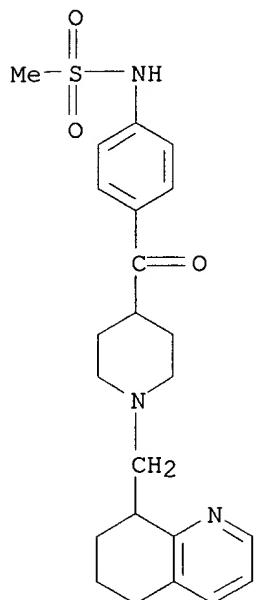


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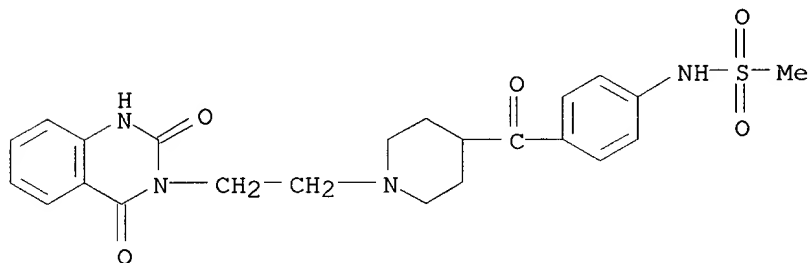
● HCl

RN 113560-13-7 HCAPLUS
CN Methanesulfonamide, N-[4-[[1-[(5,6,7,8-tetrahydro-8-quinolinyl)methyl]-4-piperidiny]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



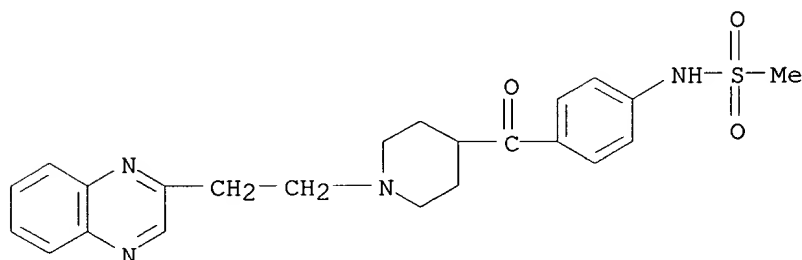
RN 113560-14-8 HCAPLUS

CN Methanesulfonamide, N-[4-[[1-[2-(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113560-15-9 HCAPLUS

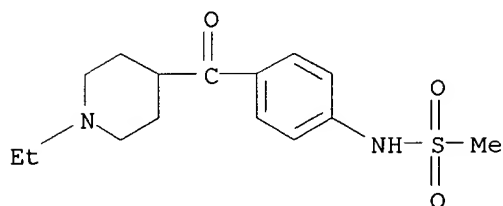
CN Methanesulfonamide, N-[4-[[1-[2-(2-quinoxaliny)ethyl]-4-piperidinyl]carbonyl]phenyl]- (9CI) (CA INDEX NAME)



RN 113560-16-0 HCAPLUS

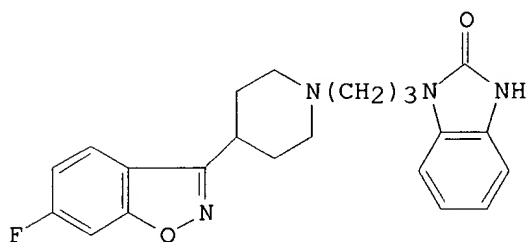
CN Methanesulfonamide, N-[4-[(1-ethyl-4-piperidinyl)carbonyl]phenyl]-, (9CI)

monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L14 ANSWER 184 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1985:203897 HCAPLUS
 DOCUMENT NUMBER: 102:203897
 TITLE: Synthesis and neuroleptic activity of
 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles
 AUTHOR(S): Strupczewski, Joseph T.; Allen, Richard C.; Gardner,
 Beth Ann; Schmid, Blaine L.; Stache, Ulrich;
 Glamkowski, Edward J.; Jones, Michael C.; Ellis,
 Daniel B.; Huger, Francis P.; Dunn, Robert W.
 CORPORATE SOURCE: Chem. Res. Dep., Hoechst-Roussel Pharm., Inc.,
 Somerville, NJ, 08876, USA
 SOURCE: J. Med. Chem. (1985), 28(6), 761-9
 CODEN: JMCMAR; ISSN: 0022-2623
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 102:203897
 GI



I

AB The synthesis of a series of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles is described. The neuroleptic activity of the series was evaluated by utilizing the climbing mice assay and inhibition of [3H]spiroperidol binding. Structure-activity relationships were studied by variation of the substituent on the benzisoxazole ring with concomitant variation of 4 different 1-piperidinyl substituents. Max. neuroleptic activity was realized when there was a 6-F substituent on the benzisoxazole ring. The 1-piperidinyl substituent appeared less significant, although in most cases, the (1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)propyl group imparted max. potency. The most potent

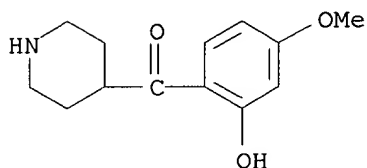
compd. in both assays was piperidinylnbenzisoazole I.

IT **84162-88-9P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 84162-88-9 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidiny-, hydrochloride (9CI)
(CA INDEX NAME)



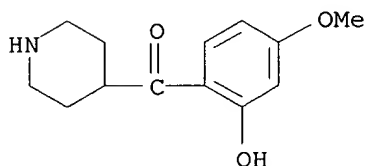
● HCl

IT **64671-19-8**

RL: RCT (Reactant)
(reaction of, with benzyl chloroformate)

RN 64671-19-8 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidiny- (9CI) (CA INDEX NAME)

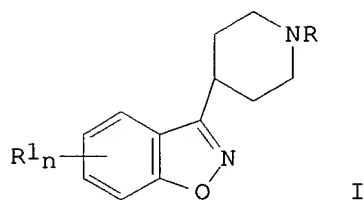


L14 ANSWER 185 OF 193 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:53870 HCAPLUS
DOCUMENT NUMBER: 98:53870
TITLE: 3-(4-Piperidyl)-1,2-benzisoazoles
INVENTOR(S): Strupczewski, Joseph T.; Gardner, Beth Ann; Allen, Richard C.
PATENT ASSIGNEE(S): Hoechst-Roussel Pharmaceuticals, Inc., USA
SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| US 4355037 | A | 19821019 | US 1981-319871 | 19811112 |
| US 4408053 | A | 19831004 | US 1982-405965 | 19820806 |
| US 4408054 | A | 19831004 | US 1982-407235 | 19820811 |
| EP 80104 | A2 | 19830601 | EP 1982-110318 | 19821109 |

Searched by Thom Larson, STIC, 308-7309

| | | | | |
|---|----|----------|-------------------|----------|
| EP 80104 | A3 | 19830824 | | |
| EP 80104 | B1 | 19881214 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE | | | | |
| AT 39251 | E | 19881215 | AT 1982-110318 | 19821109 |
| ES 517245 | A1 | 19840616 | ES 1982-517245 | 19821110 |
| CA 1215066 | A1 | 19861209 | CA 1982-415352 | 19821110 |
| AU 8290390 | A1 | 19830519 | AU 1982-90390 | 19821111 |
| AU 567865 | B2 | 19871210 | | |
| JP 58090582 | A2 | 19830530 | JP 1982-196885 | 19821111 |
| JP 04011546 | B4 | 19920228 | | |
| ZA 8208281 | A | 19830928 | ZA 1982-8281 | 19821111 |
| US 4469869 | A | 19840904 | US 1983-492846 | 19830509 |
| US 4528376 | A | 19850709 | US 1983-492767 | 19830509 |
| ES 529370 | A1 | 19850901 | ES 1984-529370 | 19840201 |
| ES 529369 | A1 | 19850916 | ES 1984-529369 | 19840201 |
| US 4408054 | B1 | 19870602 | US 1986-90001062 | 19860801 |
| AU 8811385 | A1 | 19880519 | AU 1988-11385 | 19880208 |
| AU 612621 | B2 | 19910718 | | |
| PRIORITY APPLN. INFO.: | | | US 1981-319871 | 19811112 |
| | | | US 1982-407235 | 19820811 |
| | | | EP 1982-110318 | 19821109 |
| OTHER SOURCE(S): | | | CASREACT 98:53870 | |
| GI | | | | |

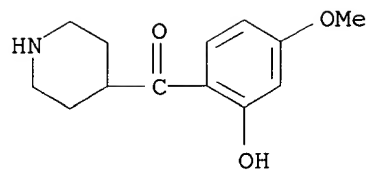


AB Analgesic benzisoxazoles I [R = H, alkyl, alkenyl, cycloalkylalkyl, phenylalkyl, HO, dialkylaminoalkyl, cyano, cyanomethyl, Bz, COR2 (R2 = H, alkyl, PhO, PhCH2O); R1 = H, alkyl, halo, HO, alkoxy; n = 1, 2] and their pharmaceutically acceptable salts were prep'd. Thus, 1-methyl-4-(2-fluorobenzoyl)piperidine was cyclized with HONH2 to give I (R = Me, R1 = H).HCl (II). The analgesic ED50 of II in the phenyl-p-quinone writhing assay in mice was 0.415 mg/kg.

IT **84162-88-9P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and reaction with benzyl chloroformate)

RN 84162-88-9 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidiny-, hydrochloride (9CI)
 (CA INDEX NAME)



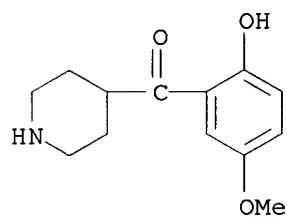
● HCl

IT 84162-89-0P 84162-92-5P 84163-56-4P

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 84162-89-0 HCAPLUS

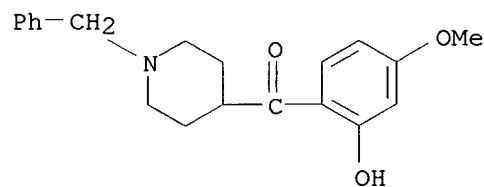
CN Methanone, (2-hydroxy-5-methoxyphenyl)-4-piperidinyloxy-, hydrobromide (9CI)
(CA INDEX NAME)



● HBr

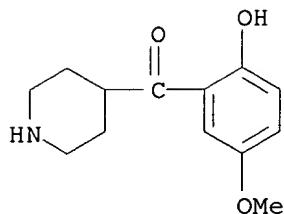
RN 84162-92-5 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl) [1-(phenylmethyl)-4-piperidinyloxy]-
(9CI) (CA INDEX NAME)



RN 84163-56-4 HCAPLUS

CN Methanone, (2-hydroxy-5-methoxyphenyl)-4-(phenylmethyl)piperidinyloxy- (9CI) (CA INDEX NAME)

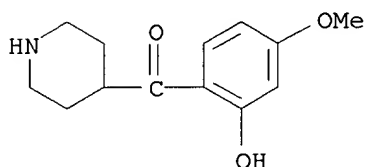
IT **64671-19-8**

RL: RCT (Reactant)

(reaction of, with benzyl chloroformate)

RN 64671-19-8 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidinyll- (9CI) (CA INDEX NAME)



L14 ANSWER 186 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1983:16716 HCAPLUS

DOCUMENT NUMBER: 98:16716

TITLE: 3-(1-Piperidinyllalkyl)-4H-pyrido[1,2-a]pyrimidin-4-one derivatives

INVENTOR(S): Kennis, Ludo E. J.; Mertens, Josephus C.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.

SOURCE: U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 134,845, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

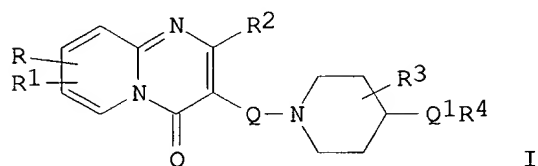
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| US 4342870 | A | 19820803 | US 1980-191632 | 19800929 |
| CA 1163994 | A1 | 19840320 | CA 1981-372258 | 19810304 |
| AU 8168429 | A1 | 19811001 | AU 1981-68429 | 19810317 |
| AU 537700 | B2 | 19840705 | | |
| SU 1068037 | A3 | 19840115 | SU 1981-3261927 | 19810324 |
| CS 256366 | B2 | 19880415 | CS 1981-2134 | 19810324 |
| JP 56150091 | A2 | 19811120 | JP 1981-42605 | 19810325 |
| JP 02015550 | B4 | 19900412 | | |
| DK 8101382 | A | 19810929 | DK 1981-1382 | 19810326 |
| DK 159390 | B | 19901008 | | |
| DK 159390 | C | 19910304 | | |
| IL 62494 | A1 | 19840831 | IL 1981-62494 | 19810326 |

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| | | | | |
|---|----|-------------------|-----------------|----------|
| FI 8100956 | A | 19810929 | FI 1981-956 | 19810327 |
| FI 71737 | B | 19861031 | | |
| FI 71737 | C | 19870209 | | |
| NO 8101058 | A | 19810929 | NO 1981-1058 | 19810327 |
| NO 156752 | B | 19870810 | | |
| NO 156752 | C | 19871118 | | |
| EP 37265 | A1 | 19811007 | EP 1981-301335 | 19810327 |
| EP 37265 | B1 | 19850123 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| ES 500814 | A1 | 19821101 | ES 1981-500814 | 19810327 |
| ZA 8102085 | A | 19821124 | ZA 1981-2085 | 19810327 |
| HU 30291 | O | 19840328 | HU 1981-783 | 19810327 |
| HU 187329 | B | 19851228 | | |
| PL 131162 | B1 | 19841031 | PL 1981-233902 | 19810327 |
| AT 11415 | E | 19850215 | AT 1981-301335 | 19810327 |
| PL 132428 | B1 | 19850330 | PL 1981-230364 | 19810327 |
| RO 82508 | P | 19830926 | RO 1981-103848 | 19810328 |
| SU 1093251 | A3 | 19840515 | SU 1982-3372597 | 19820112 |
| CA 1167843 | A2 | 19840522 | CA 1983-430092 | 19830609 |
| PRIORITY APPLN. INFO.: | | | US 1980-134845 | 19800328 |
| | | | US 1980-191632 | 19800929 |
| | | | CA 1981-372258 | 19810304 |
| | | | EP 1981-301335 | 19810327 |
| OTHER SOURCE(S): | | CASREACT 98:16716 | | |
| GI | | | | |

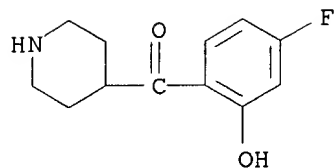


AB Serotonin antagonistic title compds. I [R, R1 = H, halo, CF3, alkyl, alkoxy; R2 = H, alkyl, alkoxy; R4 = (un)substituted Ph, thienyl, furanyl, pyridinyl; Q = alkylene; Q1 = direct bond, CO, CHOH, CH2, C:NOH, C:NNH2, acyloxymethylene, dialkoxymethylene, cyclic alkylenedioxymethylene] and their salts were prepd. Thus, refluxing 3.8 parts 3-(2-chloroethyl)-2,8-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one with 3 parts 3-(4-piperidinyl)-1H-indole, 10 parts Na2CO3 and 0.1 part KI in 240 parts Me2CHCH2COMe for 20 h gave 4.7 parts I (R = R3 = H, R1 = 8-Me, R2 = Me, R4 = 1H-indol-3-yl, Q = CH2CH2, Q1 = direct bond), which reduced, at low concns., gastric lesions in rats and contraction of caudal arteries removed from rats.

IT **81043-50-7P 81043-55-2P 81043-74-5P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)

RN 81043-50-7 HCAPLUS

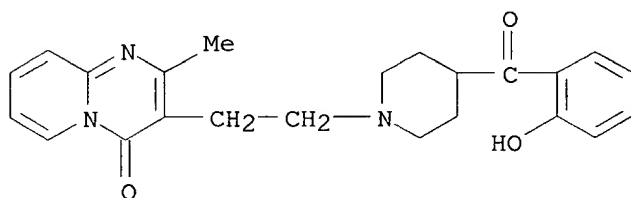
CN Methanone, (4-fluoro-2-hydroxyphenyl)-4-piperidinyl-, hydrochloride (9CI)
 (CA INDEX NAME)



● HCl

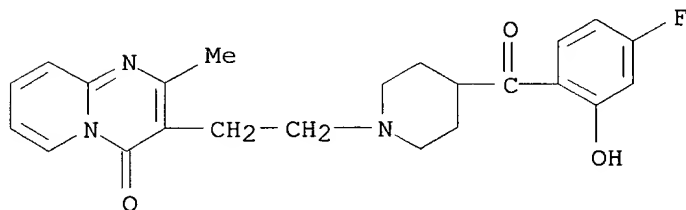
RN 81043-55-2 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(2-hydroxybenzoyl)-1-piperidinyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 81043-74-5 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L14 ANSWER 187 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1982:616203 HCAPLUS

DOCUMENT NUMBER: 97:216203

TITLE: Piperidinylalkylquinazoline compounds, composition and method of use

INVENTOR(S): Vandenberg, Jan; Kennis, Ludo; Van der Aa, Marcel; Van Heertum, Albert

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.

SOURCE: U.S., 21 pp. Cont.-in-part of U.S. Ser. No. 1,493, abandoned.

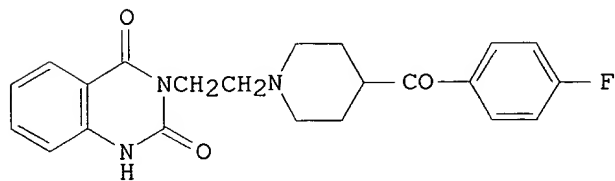
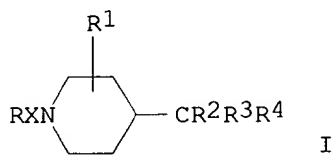
CODEN: USXXAM

Searched by Thom Larson, STIC, 308-7309

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| US 4335127 | A | 19820615 | US 1979-84272 | 19791012 |
| DK 8000072 | A | 19800709 | DK 1980-72 | 19800107 |
| DK 170669 | B1 | 19951127 | | |
| FI 8000047 | A | 19800709 | FI 1980-47 | 19800107 |
| FI 66609 | B | 19840731 | | |
| FI 66609 | C | 19841112 | | |
| NO 8000034 | A | 19800709 | NO 1980-34 | 19800107 |
| NO 155243 | B | 19861124 | | |
| NO 155243 | C | 19870304 | | |
| AU 8054381 | A1 | 19800717 | AU 1980-54381 | 19800107 |
| AU 536175 | B2 | 19840419 | | |
| EP 13612 | A2 | 19800723 | EP 1980-300059 | 19800107 |
| EP 13612 | A3 | 19801015 | | |
| EP 13612 | B1 | 19831109 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| JP 55105679 | A2 | 19800813 | JP 1980-186 | 19800107 |
| JP 63046753 | B4 | 19880919 | | |
| ZA 8000082 | A | 19810826 | ZA 1980-82 | 19800107 |
| CA 1132557 | A1 | 19820928 | CA 1980-343181 | 19800107 |
| PL 125789 | B1 | 19830630 | PL 1980-221249 | 19800107 |
| SU 1041034 | A3 | 19830907 | SU 1980-2863403 | 19800107 |
| HU 26902 | O | 19830928 | HU 1980-25 | 19800107 |
| HU 184222 | B | 19840730 | | |
| AT 5258 | E | 19831115 | AT 1980-300059 | 19800107 |
| CS 223977 | P | 19831125 | CS 1980-157 | 19800107 |
| IL 59084 | A1 | 19840229 | IL 1980-59084 | 19800107 |
| ES 487537 | A1 | 19801216 | ES 1980-487537 | 19800108 |
| RO 79148 | P | 19820817 | RO 1980-100248 | 19800220 |
| US 4522945 | A | 19850611 | US 1982-362214 | 19820326 |
| ES 527172 | A3 | 19850416 | ES 1983-527172 | 19831111 |
| PRIORITY APPLN. INFO.: | | | US 1979-1493 | 19790108 |
| | | | US 1979-84272 | 19791012 |
| | | | EP 1980-300059 | 19800107 |

OTHER SOURCE(S): CASREACT 97:216203
 GI



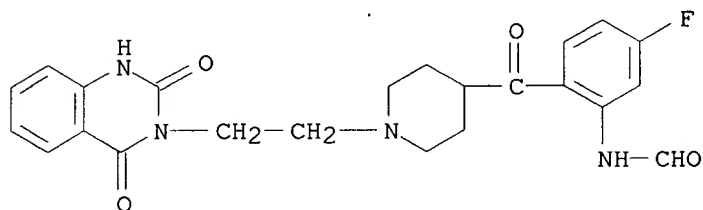
AB Piperidinylalkylquinazolines I [R = substituted quinazolinyl; R1 = H, OH, alkyl; R2 = H, R3 = H, OH; R2R3 = O, OCH2CH2O, O(CH2)3O; R4 = aryl, thienyl, pyridyl] were prepd. Thus II was obtained by treating chloroethylquinazolinedione with fluorobenzoylpiperidine. II had a serotonin antagonist ED50 in the gastric lesion test of 0.1 mg/kg orally in rats.

IT **76315-57-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cyclization of)

RN 76315-57-6 HCAPLUS

CN Formamide, N-[2-[[1-[2-(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)ethyl]-4-piperidinyl]carbonyl]-5-fluorophenyl]- (9CI) (CA INDEX NAME)

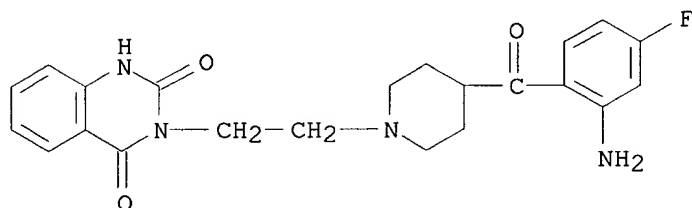


IT **76330-72-8P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 76330-72-8 HCAPLUS

CN 2,4(1H,3H)-Quinazolinedione, 3-[2-[4-(2-amino-4-fluorobenzoyl)-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 188 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1982:122814 HCAPLUS

DOCUMENT NUMBER: 96:122814

TITLE: 3-(1-Piperidinylalkyl)-4H-pyrido[1,2-a]pyrimidin-4-one derivatives

INVENTOR(S): Kennis, Ludo Edmond Josephine; Mertens, Josephus Carolus

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.

SOURCE: Eur. Pat. Appl., 47 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

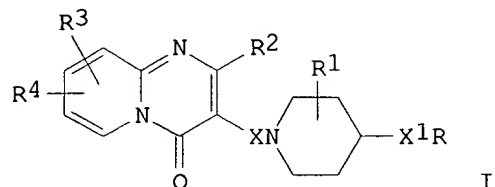
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 37265 | A1 | 19811007 | EP 1981-301335 | 19810327 |
| EP 37265 | B1 | 19850123 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| US 4342870 | A | 19820803 | US 1980-191632 | 19800929 |
| AT 11415 | E | 19850215 | AT 1981-301335 | 19810327 |
| PRIORITY APPLN. INFO.: | | | US 1980-134845 | 19800328 |
| | | | US 1980-191632 | 19800929 |
| | | | EP 1981-301335 | 19810327 |

GI



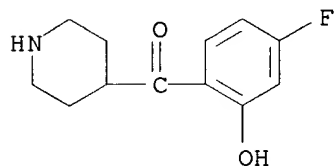
AB The title compds. I (X = alkylene; X1 = optionally ketalized CO, C:NOH, C:NNH2, optionally esterified CH2OH, CH2; R = optionally substituted Ph, thienyl, furyl, pyridinyl; R1 = H, alkyl, OH, alkoxy, CH2OH; R2 = H, alkyl, aryl; R3, R4 = H, alkyl, alkoxy, halo, CF3) were prepd. Thus 3 parts I (X = CH2CH2, X1 = CO, R = 4-FC6H4, R1 = R3 = R4 = H, R2 = Me, II) was prepd. by treating 5 parts 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one with 4.9 parts 4-(4-fluorobenzoyl)piperidine-HCl. II had a serotonin antagonist ED50 of 0.32 ng/mL in the caudal artery test in vitro.

IT **81043-50-7P 81043-55-2P 81043-74-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 81043-50-7 HCAPLUS

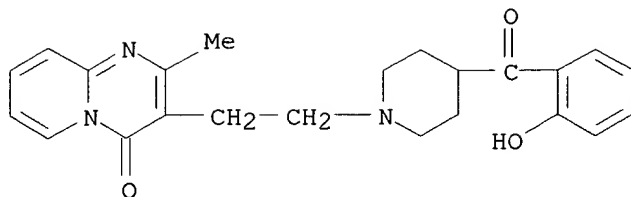
CN Methanone, (4-fluoro-2-hydroxyphenyl)-4-piperidinyl-, hydrochloride (9CI)
(CA INDEX NAME)



● HCl

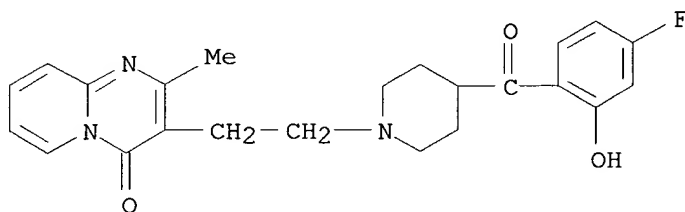
RN 81043-55-2 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(2-hydroxybenzoyl)-1-piperidinyl]ethyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 81043-74-5 HCAPLUS

CN 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L14 ANSWER 189 OF 193 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:65718 HCAPLUS

DOCUMENT NUMBER: 94:65718

TITLE: (Piperidinylalkyl)quinazoline derivatives and intermediates and pharmaceutical compositions containing them

INVENTOR(S): Vandenberg, Jan; Kennis, Ludo Edmond Josephine; Van Der Aa, Marcel Josef Maria Catharina; Van Heertum, Albert Henricus Maria Theresia

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.

SOURCE: Eur. Pat. Appl., 78 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

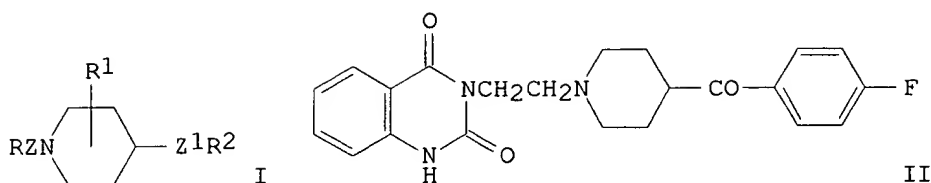
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 13612 | A2 | 19800723 | EP 1980-300059 | 19800107 |
| EP 13612 | A3 | 19801015 | | |
| EP 13612 | B1 | 19831109 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| US 4335127 | A | 19820615 | US 1979-84272 | 19791012 |
| AT 5258 | E | 19831115 | AT 1980-300059 | 19800107 |
| PRIORITY APPLN. INFO.: | | | US 1979-1493 | 19790108 |
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| | | | EP 1980-300059 | 19800107 |

Searched by Thom Larson, STIC, 308-7309

GI



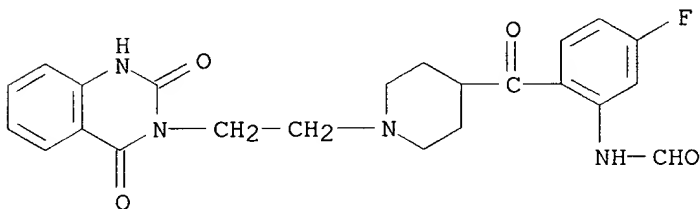
AB The title compds. I [R = a 1-, 2-, 3-, or 4-quinazolinyl group (the pyrimidine ring is partly or fully satd., the quinazoline ring system contains an oxo or thioxo group in the 2- and/or 4-positions, the fused benzo is optionally substituted by halo, alkyl, alkoxy, CF₃, NO₂, or cyano); Z = C1-4 alkylene; R₁ = H, OH, alkyl; Z₁ = CO, CH(OH), CH(O₂CR₃) (R₃ = H, alkyl), CH₂, C(OR₄)₂ (R₄ = alkyl), 1,3-dioxolane-2,2-diyl, 1,3-dioxane-2,2-diyl, C(:NOH), C(:NNH₂); R₂ = Ph, halo-, alkyl-, alkoxy-, (trifluoromethyl)-, or aminophenyl, thienyl, pyridyl], which showed serotonin antagonist activity, were prepd. by different methods. Thus, 3-(2-chloroethyl)-2,4(1H, 3H)-quinazolinedione was heated with 4-(4-fluorobenzoyl)piperidine-HCl and Na₂CO₃ in Me₂CHCH₂CO₂Me to give II.

IT **76315-57-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (prepn. and deformylation of)

RN 76315-57-6 HCAPLUS

CN Formamide, N-[2-[[1-[2-(1,4-dihydro-2,4-dioxo-3(2H)-quinazolinyl)ethyl]-4-piperidinyl]carbonyl]-5-fluorophenyl]- (9CI) (CA INDEX NAME)

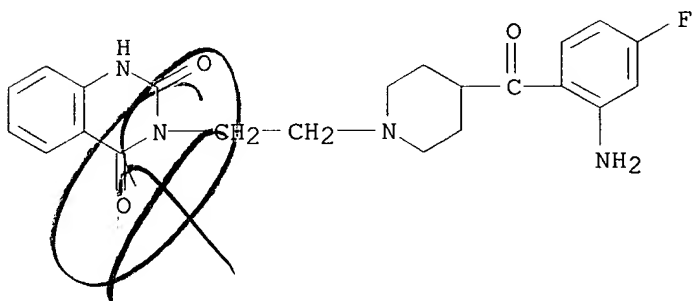


IT **76330-72-8P**

RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. and use of, as serotonin antagonist)

RN 76330-72-8 HCAPLUS

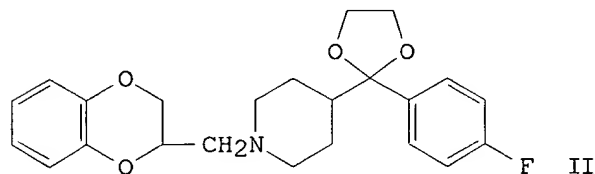
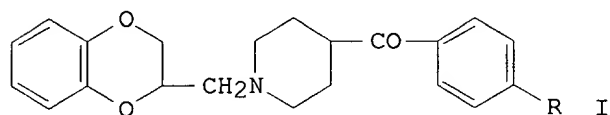
CN 2,4(1H,3H)-Quinazolinedione, 3-[2-[4-(2-amino-4-fluorobenzoyl)-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



L14 ANSWER 190 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1981:65700 HCAPLUS
 DOCUMENT NUMBER: 94:65700
 TITLE: Benzodioxane derivatives
 PATENT ASSIGNEE(S): Bouchara, Emile, Fr.
 SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| JP 55111482 | A2 | 19800828 | JP 1979-16763 | 19790217 |

GI



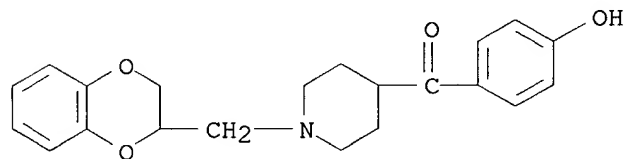
AB Benzodioxane derivs. (I; R = H, halo, OH, C1-6 alkyl, alkoxy, acyloxy), effective antihypertensives at 10-50 mg/kg in rats and dogs, were prepd. Thus, 100 parts II.HCl and 200 parts concd. HCl in aq. Me₂CHOH was heated to boiling for 2.5 h to give 74 parts I (R = F). Similarly prepd. were 7 addnl. I and salts.

IT **76335-57-4P 76335-58-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)

RN 76335-57-4 HCAPLUS

CN Methanone, [1-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-4-piperidinyl](4-hydroxyphenyl)- (9CI) (CA INDEX NAME)

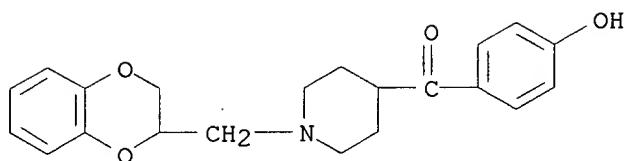


RN 76335-58-5 HCAPLUS

CN 3-Pyridinecarboxylic acid, compd. with [1-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-4-piperidinyl](4-hydroxyphenyl)methanone (1:1) (9CI) (CA INDEX NAME)

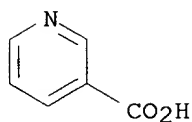
CM 1

CRN 76335-57-4
CMF C21 H23 N O4



CM 2

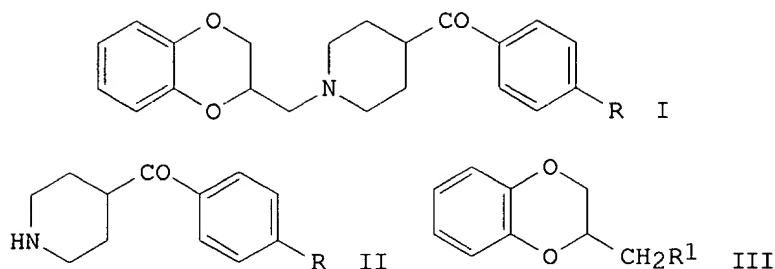
CRN 59-67-6
CMF C6 H5 N O2



L14 ANSWER 191 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1981:65699 HCAPLUS
 DOCUMENT NUMBER: 94:65699
 TITLE: Benzodioxan derivatives and their therapeutical applications
 INVENTOR(S): Dumaitre, Bernard; Perrin, Claude; Cornu, Pierre Jean; Streichenberger, Gilles
 PATENT ASSIGNEE(S): Bouchara, Emile, Fr.
 SOURCE: Eur. Pat. Appl., 18 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------|------|----------|-----------------|----------|
| EP 14295 | A1 | 19800820 | EP 1979-400071 | 19790205 |
| EP 14295 | B1 | 19830119 | | |
| R: BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| CA 1119602 | A1 | 19820309 | CA 1979-321394 | 19790213 |
| US 4432984 | A | 19840221 | US 1981-269411 | 19810601 |
| PRIORITY APPLN. INFO.: | | | EP 1979-400071 | 19790205 |
| | | | US 1979-11162 | 19790209 |
| | | | US 1980-134476 | 19800327 |

GI



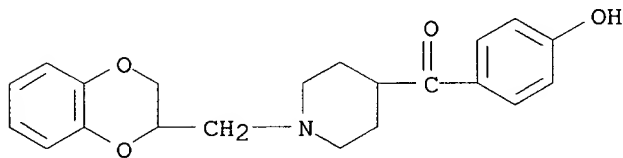
AB Benzodioxins I (R = H, halo, C1-6 alkyl, HO, C1-6 alkoxy, acyloxy), useful as antihypertensives, were prepd. by condensation of benzoylpiperidines II and methylbenzodioxins III (R₁ = Cl or reactive ester). Thus, II (R = MeO) and III (R₁ = MeSO₃) in xylene contg. K₂CO₃ was refluxed to give I (R = MeO), which was converted to its fumarate.

IT **76335-57-4P 76335-58-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 76335-57-4 HCAPLUS

CN Methanone, [1-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-4-piperidinyl](4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



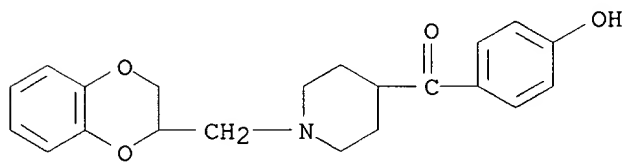
RN 76335-58-5 HCAPLUS

CN 3-Pyridinecarboxylic acid, compd. with [1-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-4-piperidinyl](4-hydroxyphenyl)methanone (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 76335-57-4

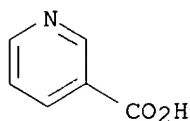
CMF C21 H23 N O4



CM 2

CRN 59-67-6

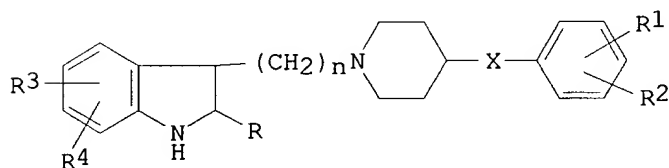
CMF C6 H5 N O2



L14 ANSWER 192 OF 193 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1978:190589 HCAPLUS
 DOCUMENT NUMBER: 88:190589
 TITLE: Benzoylpiperidylalkylindoles
 PATENT ASSIGNEE(S): Hoechst A.-G., Fed. Rep. Ger.
 SOURCE: Neth. Appl., 33 pp.
 CODEN: NAXXAN
 DOCUMENT TYPE: Patent
 LANGUAGE: Dutch
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| NL 7702534 | A | 19770916 | NL 1977-2534 | 19770309 |
| CA 1078387 | A1 | 19800527 | CA 1977-273782 | 19770311 |
| CH 635584 | A | 19830415 | CH 1977-3128 | 19770311 |
| BE 852431 | A1 | 19770914 | BE 1977-175762 | 19770314 |
| US 4110459 | A | 19780829 | US 1977-808513 | 19770621 |
| CH 638201 | A | 19830915 | CH 1981-4617 | 19810714 |
| PRIORITY APPLN. INFO.: | | | US 1976-663820 | 19760314 |
| | | | US 1975-594042 | 19750708 |
| | | | CH 1977-3128 | 19770311 |

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I

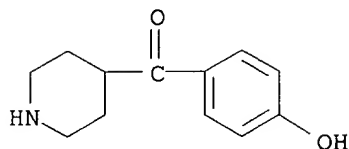
AB Piperidylalkylindoles I (X = CO, CHO; R, R3, R4 = H, Me; R1, R2 = H, halogen, C1-5 alkyl, alkoxy, CF3, OH, OPh, Ph; n = 2, 3) were prepd. Thus isonipecotic acid was acetylated and chlorinated to give 1-acetylisonipecotoyl chloride, which was used for Friedel-Crafts acylation of PhF. The resulting 1-acetyl-4-(4-fluorobenzoyl)piperidine was hydrolyzed to give 4-(4-fluorobenzoyl)piperidine-HCl, which was treated with 3-(2-bromoethyl)indole to give I (R = R1 = R3 = R4 = H, R2 = 4-F, X = CO, n = 2, II). II was tranquilizing at 10 mg/kg and had an analgesic ED50 of 4.4 mg/kg in mice. Some I also had antihypertensive activity.

IT **64671-07-4P 64671-19-8P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and reaction of, with bromoethylindole)

RN 64671-07-4 HCAPLUS

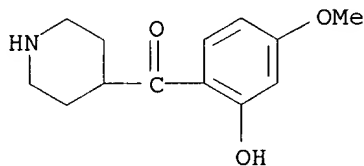
CN Methanone, (4-hydroxyphenyl)-4-piperidiny-, hydrobromide (9CI) (CA INDEX NAME)



● HBr

RN 64671-19-8 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidiny- (9CI) (CA INDEX NAME)

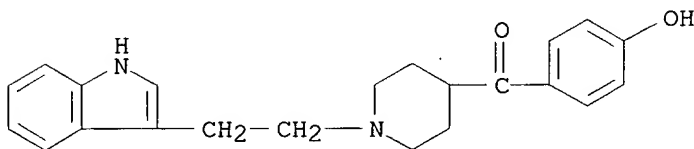


IT **64671-08-5P 64671-20-1P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

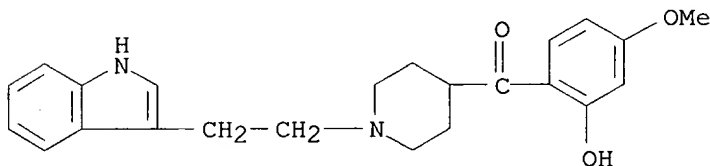
RN 64671-08-5 HCAPLUS

CN Methanone, (4-hydroxyphenyl) [1-[2-(1H-indol-3-yl)ethyl]-4-piperidiny]- (9CI) (CA INDEX NAME)



RN 64671-20-1 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl) [1-[2-(1H-indol-3-yl)ethyl]-4-piperidiny]- (9CI) (CA INDEX NAME)



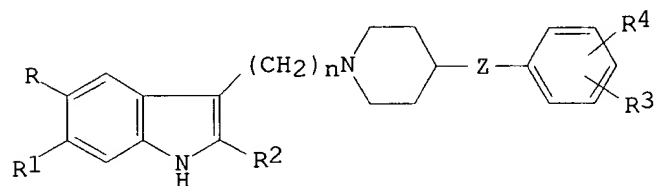
L14 ANSWER 193 OF 193 HCAPLUS COPYRIGHT 2002 ACS

Searched by Thom Larson, STIC, 308-7309

ACCESSION NUMBER: 1977:601332 HCAPLUS
 DOCUMENT NUMBER: 87:201332
 TITLE: Benzoylpiperidylalkylindoles
 INVENTOR(S): Helsley, Grover Cleveland; Gardner, Beth Ann;
 Strupczewski, Joseph Thomas
 PATENT ASSIGNEE(S): Hoechst A.-G., Fed. Rep. Ger.
 SOURCE: Ger. Offen., 33 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| DE 2708913 | A1 | 19770908 | DE 1977-2708913 | 19770302 |
| CA 1078387 | A1 | 19800527 | CA 1977-273782 | 19770311 |
| CH 635584 | A | 19830415 | CH 1977-3128 | 19770311 |
| BE 852431 | A1 | 19770914 | BE 1977-175762 | 19770314 |
| US 4110459 | A | 19780829 | US 1977-808513 | 19770621 |
| CH 638201 | A | 19830915 | CH 1981-4617 | 19810714 |
| PRIORITY APPLN. INFO.: | | | US 1976-663820 | 19760304 |
| | | | US 1975-594042 | 19750708 |
| | | | CH 1977-3128 | 19770311 |

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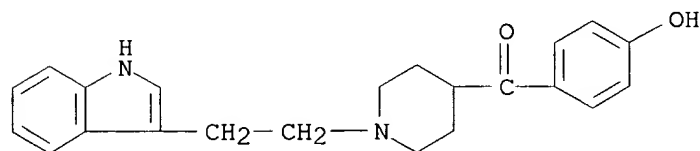
AB The title compds. I ($R = R_1 = H, MeO$; $R_2 = H, Me$; $R_3 = R_4 = H, F, OH, OMe, CMe_3$, etc.; $n = 2, 3$; $Z = CHOH, CO$) were prepd. Thus, 3-(2-bromoethyl)indole was treated with 4-(4-fluorobenzoyl)piperidine (II) in $K_2CO_3/BuOH$ to give I ($R = R_1 = R_2 = R_3 = H, R_4 = 4-F, n = 2, Z = CO$) (III). Isonipecotinic acid was N-acetylated and converted to the acid chloride which was treated with PhF and deacetylated to give II. I are useful as sedatives, e.g., III has ED_{50} 10 mg/kg in mice.

IT **64671-08-5P 64671-20-1P**

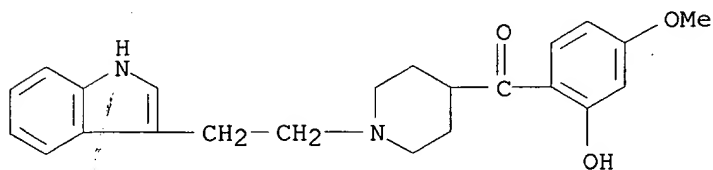
RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of)

RN 64671-08-5 HCAPLUS

CN Methanone, (4-hydroxyphenyl)[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]-(9CI) (CA INDEX NAME)



RN 64671-20-1 HCAPLUS
 CN Methanone, (2-hydroxy-4-methoxyphenyl) [1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]- (9CI) (CA INDEX NAME)

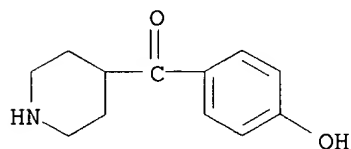


IT 64671-07-4P 64671-19-8P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, and reaction with bromoethylindole)

RN 64671-07-4 HCAPLUS

CN Methanone, (4-hydroxyphenyl)-4-piperidinyl-, hydrobromide (9CI) (CA INDEX NAME)



● HBr

RN 64671-19-8 HCAPLUS

CN Methanone, (2-hydroxy-4-methoxyphenyl)-4-piperidinyl- (9CI) (CA INDEX NAME)

